

I. A Study of the Action of Primary and
Tertiary Amines on Camphor-
oxalic Acid.

II. A Study of the Action of Certain
Secondary Amines on Camphor-
oxalic Acid.

III. Acyl Derivatives of Ortho- and
Paraminophenol.

DISSERTATION

SUBMITTED TO THE BOARD OF UNIVERSITY STUDIES OF
THE JOHNS HOPKINS UNIVERSITY IN CONFORMITY
WITH THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY.

BY

L. F. WILLIAMS.

EASTON, PA. :
ESCHENBACH PRINTING COMPANY.
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CONTENTS.

Acknowledgment.....	4
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PART I.

A Study of the Action of Primary and Tertiary Amines on Camphor-oxalic Acid.....	5
Introduction.....	5
Theoretical:	
Primary Amines.....	10
Tertiary Amines.....	12
Table of Compounds.....	14
Experimental:	
Primary Amines.....	16
Tertiary Amines.....	21

PART II.

A Study of the Action of Certain Secondary Amines on Camphoroxalic Acid.....	29
Theoretical.....	29
Table of Compounds.....	37
Experimental:	38

PART III.

Acyl Derivatives of Ortho- and Paraminophenol.....	49
Introductory.....	49
Table of Compounds.....	56
Experimental:	
Preparation of Orthoacetoaminophenol.....	57
Action of Acyl Chlorides on Orthoaminophenol Hydrochloride..	58
Preparation of Paracetoaminophenol.....	63
Action of Acyl Chlorides on Paraminophenol Hydrochloride...	65
Conclusions.....	71
Biographical.....	72

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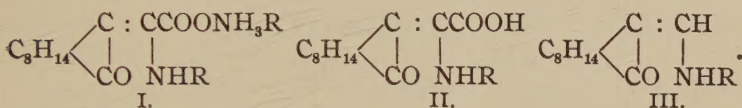
The author takes pleasure in expressing his gratitude to President Remsen, Professor Morse, Professor Jones, and Professor Mathews for instruction received from them, and especially to Professor J. Bishop Tingle, under whose direction this investigation has been pursued, for guidance in the work and for his personal interest.

PART I.

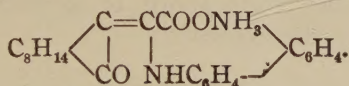
Study of the Action of Primary and Tertiary Amines on Camphor-oxalic Acid.

THEORETICAL.

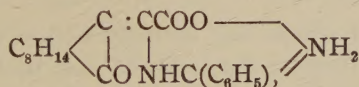
In a series of papers by J. Bishop Tingle and his co-workers it has been shown that camphoroxalic acid combines with a number of primary amines to form condensation products which usually belong to the three types,



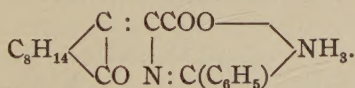
In the case of some amines which contain more than one amino group, such as benzidine,¹ the compound, though apparently different from the above typical forms, is probably fundamentally similar, one amino group condensing and one neutralizing the carboxyl, as expressed by the formula



The product formed with benzamidine² is probably essentially similar in constitution,



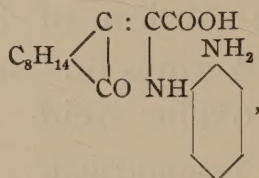
or



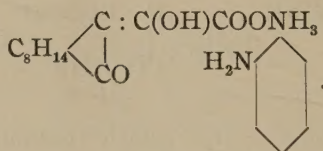
¹ Am. Chem. J., **34**, 231 (1905).

² J. Amer. Chem. Soc., **23**, 375 (1901).

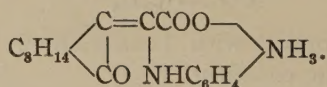
In the case of orthophenylenediamine¹ another complication is encountered. It is evident that a compound of type II



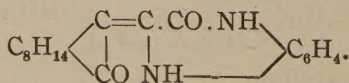
would be extremely likely to combine further to form a five-membered ring, and that the same would, of course, be true if the amino group first attacked the carboxyl, as in the case of a substance with the structure



Experiment showed that this actually took place because, in spite of many attempts to do so, it was not found to be possible to isolate any compound corresponding to either of the two formulae given above, or to such a substance as is represented by the expression

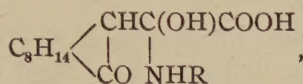


The compound which was actually obtained, as the result of a number of experiments carried out under very varied conditions, was the quinoxaline derivative,



¹ Am. Chem. J., 34, 230 (1905).

The formation, primarily, in all these cases, of an addition compound,



is, of course, assumed. A number of such additive products from primary amines have been definitely isolated and studied by Bishop Tingle, alone, and in conjunction with Alfred Tingle, W. E. Hoffman, Jr., and C. J. Robinson.¹

Their constitution and the bearing which their formation has on the ketonic-enolic question have been fully considered and discussed.² A number of addition compounds of camphoroxalic acid and secondary amines have been described by Bishop Tingle and W. E. Hoffman, Jr.,³ and also by Bishop Tingle and me.⁴

Returning, now, to the substances belonging to the three types formulated above, there are two points which call for comment. A given amine is not necessarily capable of forming compounds belonging to each of these classes; some can do so, others only yield two, and certain amines appear to be able to give not more than one of them; in this latter event it is usually the substance belonging to type three which is formed. I shall return to this point after presenting my own results.

An inspection of the amines hitherto employed for the condensations discloses the fact that a considerable number have failed to react at all with camphoroxalic acid. It is obvious that the cause of this failure must be cleared up before it will be possible to formulate the regularity underlying the reactions in question. Further, it is desirable to increase the available data by extending the experiments so as to include a larger number of amines within the scope of the investigation. This was, therefore, my first object in under-

¹ *Loc. cit.*

² *Vide*, especially, Am. Chem. J., **36**, 223 (1906).

³ *Ibid.*, **34**, 217 (1905).

⁴ *Ibid.*, **39**, 122 (1908). Cf. O. Dimroth: Ber. d. chem. Ges., **40**, 2404 (1907).

taking the investigation whose results are recorded in the present dissertation.

The readiness with which aniline reacts with camphor-oxalic acid,¹ and the difficulty experienced in obtaining condensation products with paranitraniline, on the one hand, and with para- and metaphenylenediamine² on the other, made it desirable to investigate the behavior of the aminophenols in this connection, because these latter compounds might be regarded as being in a position midway between the substances in question. They are less basic than aniline, but more so than the nitranilines. They are disubstituted compounds like the nitranilines and phenylenediamines, but, in the case of the aminophenols, a condensation, in addition to salt formation, is highly improbable. This latter point is of some importance, because it has been shown by Bishop Tingle, in conjunction, with Messrs. Cram³ and Lovelace,⁴ that salt formation is, in some cases, an important factor in promoting intramolecular condensations.

The objection might be raised that there is nothing to prevent the aminophenols from first forming salts which could afterwards undergo rearrangement and condensation. The answer to this is found in the work of Bishop Tingle and Alfred Tingle⁵ on the compounds of aniline and camphoroxalic acid, and especially in their results with *o*-phenylenediamine. They found that this base gave the compound mentioned above, alike from the free acid, its sodium salt, or from ethyl camphoroxalate. The same point is demonstrated by my own results with benzalaniline and camphoroxalic acid, cf. p. 13.

Assuming, then, that the amino groups of ortho- and para-aminophenol combine in the regular manner with camphor-oxalic acid, it is at least conceivable that the resulting substances,

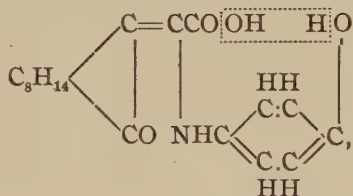
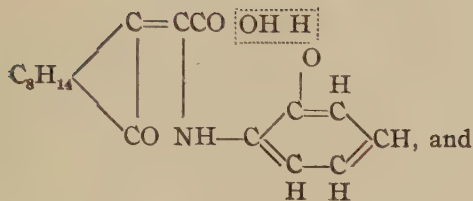
¹ Am. Chem. J., **21**, 238 (1899).

² *Ibid.*, **34**, 253 (1905).

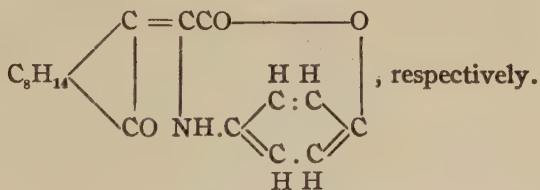
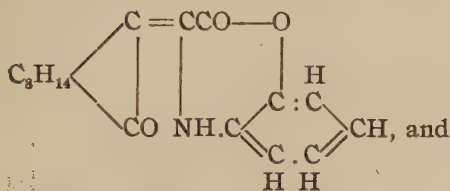
³ *Ibid.*, **37**, 596 (1907).

⁴ *Ibid.*, **38**, 642 (1907).

⁵ *Loc. cit.*



might eliminate the elements of water, as shown by the dotted lines in the preceding formulae or in some other manner, giving rise, finally, to the compounds



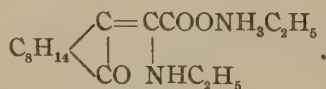
Clearly, such a double condensation, if it could occur at all, would, doubtless, depend essentially on the possibility of forming new cycloids of the maximum stability, *i. e.*, those containing five or six members. As will be seen from a later part of this dissertation, these ideas have been realized in the case of orthoaminophenol, whereas, in the case of the para compound, two molecules combined with one of the acid, the product being a salt of an addition product.

In connection with another line of work, it appeared to be desirable to investigate the behavior of camphoroxalic acid toward certain *tertiary bases*, especially those of an alkaloidal nature, the particular object being to obtain salts with well developed crystallizing power, which might ultimately prove of service in the examination of camphoroxalic acid for possible stereo- or structural isomers. My results in this connection are discussed later in the present dissertation.

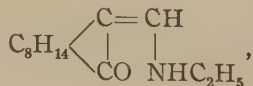
In previous communications on this subject¹ the interaction of camphoroxalic acid with methylamine, α -naphthylamine, β -naphthylamine, paratoluidine, metatoluidine, benzylamine, benzamidine, benzidine, 1,2,4-nitrotoluidine, orthophenylenediamine, aniline, semicarbazine, dimethylamine, diethylamine, hydroxylamine, ammonia, phenylhydrazine, urea, methylurea, symmetrical dimethylurea, unsymmetrical dimethylurea, hydrazine, and parabromophenylhydrazine has been studied. I have now supplemented this by the investigation of the following substances:

PRIMARY AMINES.

1. *Ethylamine*.—Ethylamine gives *ethylamine ethylcamphorformeneaminecarboxylate*,



When this salt is heated considerably above its melting point, *ethylcamphorformeneamine*,

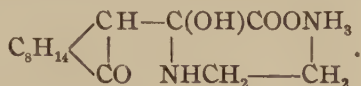


is formed.

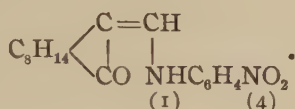
2. *Ethylenediamine*.—Ethylenediamine gives a product resembling the direct addition products of primary amines with this acid which have been described by Bishop Tingle

¹ *Loc. cit.*

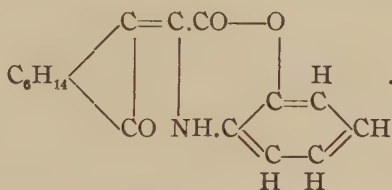
and his colleagues,¹ and is, accordingly, a *camphoformolamine derivative*, represented by the formula



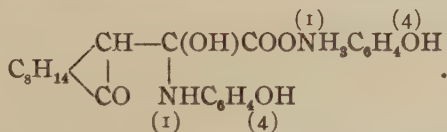
3. *Paranitraniline*.—Paranitraniline gives *paranitrophenylcamphoformeneamine*,



4. *Orthoaminophenol*.—Orthoaminophenol gives the lactone of *orthohydroxyphenylcamphoformeneaminecarboxylic acid*,



5. *Paraminophenol*.—Paraminophenol gives *paraminophenol parahydroxyphenylcamphoformolaminecarboxylate*,

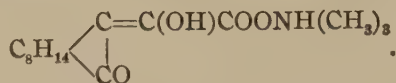


Attempts were made to obtain compounds of camphor-oxalic acid with *n*-propylamine (6), *metaphenylenediamine* (7), and *paraphenylenediamine* (8), but without success. Reaction appears to take place in each case, but the products cannot be purified by any of the ordinary methods. Even had it been worth while, time was lacking to devise a special mode of isolation for each compound.

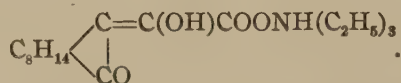
¹ *Loc. cit.*

TERTIARY AMINES.

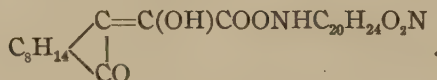
9. *Trimethylamine*.—Trimethylamine gives *trimethylamine camphoroxalate*,



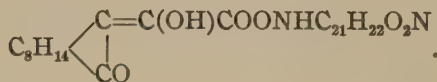
10. *Triethylamine*.—Triethylamine yields *triethylamine camphoroxalate*,



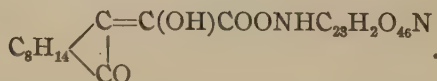
11. *Quinine*.—Quinine forms *quinine camphoroxalate*,



12. *Strychnine*.—Strychnine gives *strychnine camphoroxalate*,

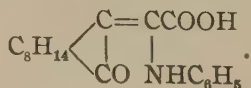


13. *Brucine*.—Brucine yields *brucine camphoroxalate*,



Attempts to prepare two isomeric compounds were unsuccessful.

14. *Benzalaniline*.—Benzalaniline gives *phenylcamphorformeneaminocarboxylic acid*,



Its production is evidently due to a hydrolysis of the benzal-aniline into benzaldehyde and aniline, under the influence of the acid and of a trace of water in the reacting materials. As the reaction proceeded the quantity of water would, of course, increase steadily, because it is necessarily formed as a result of the condensation. The presence of benzaldehyde among the products of the reaction was proved by its odor.

The formation of the above condensation product demonstrates once more, in the clearest manner, the superior reactivity of the enolic group $C:COH$, as compared with the carboxylic group, *i. e.*, even with relatively strong bases, if other conditions are favorable, condensation, rather than salt formation, takes place. Cf. p. 8.

15. *Piperine*.—Piperine gave only a small amount of piperic acid, owing, probably, to the presence of a little moisture in the reagents.

16. *Tribenzylamine*.—Attempts to obtain a crystalline salt of tribenzylamine and camphoroxalic acid were unsuccessful.

It is evident that, of the salts described above, those of brucine and strychnine appear to be admirably adapted for the investigation of possible isomeric forms of camphoroxalic acid. This matter will receive attention in the near future.

17. *Tetraethylammonium Hydroxide*.—Tetraethylammonium hydroxide gave a crystalline salt, but it was too unstable to permit of complete purification.

The following table (pp. 14-15) shows the various condensation compounds of camphoroxalic acid and primary amines which have been prepared by Bishop Tingle and his co-workers¹ and also those which are described for the first time in this dissertation. The former are indicated by an asterisk (*). Those marked + contain the elements of 1 molecule of water more than is shown by the type formula. When no definite compound could be isolated the space in the table is occupied by a dash.

¹ *Loc. cit.*

Primary amine.		I.	II.	III.
1	NH ₃	$\begin{array}{c} \text{C}=\text{CCO}_2\text{NH}_3\text{R} \\ \\ \text{C}_8\text{H}_{14} \end{array}$	$\begin{array}{c} \text{C}=\text{CCO}_2\text{H} \\ \\ \text{C}_8\text{H}_{14} \end{array}$	$\begin{array}{c} \text{C}=\text{CH} \\ \\ \text{C}_8\text{H}_{14} \end{array}$
2	NH ₂ OH		*178°	
3	CH ₃ NH ₂	*172°	+*146°.5	*131°
4	C ₂ H ₅ NH ₂	109°		118°
5	n-C ₇ H ₇ NH ₂	Gum was formed		
6	H ₂ NNH ₂	$\begin{array}{c} \text{CO} \\ \\ \text{C}_8\text{H}_{14} \end{array}$	$\begin{array}{c} \text{C}:\text{C}(\text{OH})\text{CO}_2\text{NH}_3 \\ \\ \text{C}_8\text{H}_{14} \end{array}$	*186°
7	OC(NH ₂) ₂	*192°-194°	$\begin{array}{c} \text{C}:\text{C}(\text{OH})\text{CO}_2\text{NH}_3 \\ \\ \text{C}_8\text{H}_{14} \end{array}$	
8	CH ₃ NHCONH ₂	$\begin{array}{c} \text{C}:\text{CCO}_2\text{H} \\ \\ \text{C}_8\text{H}_{14} \end{array}$	$\begin{array}{c} \text{C}:\text{CCO}_2\text{H} \\ \\ \text{C}_8\text{H}_{14} \end{array}$	*154°
9	(CH ₃) ₂ NCONH ₂		$\begin{array}{c} \text{N}-\text{CO} \\ \\ \text{C}_8\text{H}_{14} \end{array}$	
10	H ₂ NCH ₂ CH ₂ NH ₂		+220°	
11	H ₂ NCONHNH ₂		*198°	
12	C ₆ H ₅ CH ₂ NH ₂	*147°.5	*140°	*96°.5
13	C ₆ H ₅ NH ₂	*158°	*174°	*166°
14	CH ₃ C ₆ H ₄ NH ₂ (1:2)			

Primary amine.

15	$\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2(1:3)$	I. $\begin{array}{c} \text{C}=\text{CCO}_2\text{NH}_2\text{R} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_{14} \quad \text{CO NHR} \end{array}$	II. $\begin{array}{c} \text{C}=\text{CCO}_2\text{H} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_{14} \quad \text{CO NHR} \end{array}$	III. $\begin{array}{c} \text{C}=\text{CH} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_{14} \quad \text{CO NHR} \end{array}$
16	$\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2(1:4)$	*126° *152°	*154° *168°	 *178°
17	$\text{HOC}_6\text{H}_4\text{NH}_2(1:2)$	$\begin{array}{c} \text{C}=\text{CCO}- \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_{14} \quad \text{CO} \end{array}$ + 190° $\text{C}_{18}\text{H}_{22}\text{O}_2\text{N}_2$	$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{C}=\text{CCO}- \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_{14} \quad \text{HNC}_6\text{H}_4 \end{array}$ 178° *246°	*159° .5 314° 156° *192° *190° *173°
18	$\text{HOC}_6\text{H}_4\text{NH}_2(1:4)$			
19	$\text{C}_6\text{H}_4(\text{NH}_2)_2(1:2)$			
20	$\text{C}_6\text{H}_4(\text{NH}_2)_2(1:3)$			
21	$\text{C}_6\text{H}_4(\text{NH}_2)_2(1:4)$			
22	$\text{O}_2\text{NC}_6\text{H}_4\text{NH}_2(1:4)$			
23	$\text{CH}_3\text{COC}_6\text{H}_4\text{NH}_2(1:4)$			
24	$\text{CH}_3\text{C}_6\text{H}_3(\text{NO}_2)\text{NH}_2(1:2:4)$			
25	$\text{C}_6\text{H}_5\text{NHNH}_2$			
26	$\text{BrC}_6\text{H}_4\text{NHNH}_2(1:4)$			
27	$\text{C}_6\text{H}_5\text{C}(:\text{NH})\text{NH}_2$	$\text{C}_{19}\text{H}_{24}\text{O}_2\text{N}_2$ *120° + *149° *184°	$\begin{array}{c} \text{C}=\text{CCO}_2-\text{NH}_3 \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_{14} \quad \text{CO} \end{array}$ *165° *169°	 *190° *172° .5
28	$\text{H}_2\text{NC}_6\text{H}_4\text{C}_6\text{H}_4\text{NH}_2(1:4)$			
29	$\alpha\text{-C}_{10}\text{H}_7\text{NH}_2$			
30	$\beta\text{-C}_{10}\text{H}_7\text{NH}_2$			

EXPERIMENTAL.

In the preparation of camphoroxalic acid the method used was that described by J. Bishop Tingle and W. E. Hoffman, Jr.,¹ with the changes which were suggested and employed by J. Bishop Tingle and C. J. Robinson.²

PRIMARY AMINES.

1. *Ethylamine*.—Ethylamine (5 grams = 2 mol.) and camphoroxalic acid (12.5 grams = 1 mol.) were placed in a pressure bomb with 30 cc. of absolute ethyl alcohol and heated to 100° for six hours. The bomb was opened after cooling and the excess of solvent evaporated. A semicrystalline mass was left which, on dissolving in gasolin and adding chloroform, separated from the solution in a fairly pure condition. The compound was purified by recrystallization from ethyl acetate, being deposited in white needles, which melt at 109°. When dissolved in alcohol and ferric chloride added, no color is produced. Analysis showed the compound to be *ethylamine ethylcamphoformeneaminecarboxylate*.

Analysis:

0.2303 gram substance gave 19.2 cc. N at 24° and 760 mm.

N	Calculated for	Found.
	$\begin{array}{c} \text{C}_8\text{H}_{14} \begin{array}{l} \nearrow \text{C} = \text{CCOONH}_2\text{C}_2\text{H}_5 \\ \searrow \text{CO} \quad \\ \quad \text{NHC}_2\text{H}_5 \end{array} \end{array}$	
	9.47	9.13

When treated with sodium hydroxide the above salt dissolves but, on acidification with dilute hydrochloric acid, decomposes into camphoroxalic acid and ethylamine.

When heated at 150° *ethylamine ethylcamphoformeneaminecarboxylate* gives off carbon dioxide and ethylamine and forms a compound which, when recrystallized from acetone, is deposited in semitransparent plates, melting at 118°. With alcoholic ferric chloride no color reaction is produced. Analysis proved this compound to be *ethylcamphoformeneamine*.

¹ Am. Chem. J., **34**, 235 (1905).

² *Ibid.*, **35**, 248 (1906).

Analysis:

0.1135 gram substance gave 7.0 cc. N at 24° and 755 mm.

	Calculated for	
	$\begin{array}{c} \text{C}=\text{CH} \\ \diagup \quad \diagdown \\ \text{C}_8\text{H}_{14} \quad \text{CO} \quad \text{NHC}_2\text{H}_5 \end{array}$	
N	6.77	Found. 6.70

2. *Ethylenediamine*.—The free base was prepared as follows: Ethylenediamine hydrochloride (5 grams = 1 mol.) was dissolved in absolute methyl alcohol. To this was added an similar solution of potassium hydroxide containing 42 grams = 2 mol. The alcoholic solution of the base was filtered from the potassium chloride and to the solution camphoroxalic acid (8.4 grams = 1 mol.) was added and the liquid heated for a short time. Crystals began to form and the solution was concentrated further in a vacuum desiccator. The compound was purified by crystallization from a mixture of 60 parts of methyl alcohol and 40 parts of water, being deposited in greyish-white, microscopic crystals, melting at 220°. It is sparingly soluble in ethyl acetate, acetone, benzene, toluene, ether, and in ethyl and methyl alcohols. Analysis showed the substance to be an additive compound similar to the body obtained by Bishop Tingle¹ from hydroxylamine and camphoroxalic acid, and it belongs to the *camphorformolamine series*.

Analysis:

0.1816 gram compound gave 15.3 cc. N at 770 mm. and 20°.

	Calculated for	
	$\begin{array}{c} \text{CHC}(\text{OH})\text{CO}_2\text{NH}_3\text{C}_2\text{H}_4\text{NH}_2 \\ \diagup \quad \diagdown \\ \text{C}_8\text{H}_{14} \quad \text{CO} \end{array}$	
N	9.87	Found. 9.58

When the above compound is heated at 215°, water and carbon dioxide are given off and a dark gummy mass is left in the tube. A semicrystalline mass was separated from this but no crystals free from gum could be obtained, so that no attempt was made to analyze the compound. The gummy mass gave no color reaction with alcoholic ferric chloride.

¹ *Loc. cit.*

3. *Paranitraniline*.—Paranitraniline (4.15 grams = 1 mol.), camphoroxalic acid (6.75 grams = 1 mol.), and benzene (30 cc.) were heated, under pressure, at 135°-140°, for six hours. When the bomb was opened, after cooling, there was considerable internal pressure. The benzene was evaporated and a tarry mass was formed. As no crystals could be separated from this tar by dissolving it in various solvents, it was treated with a dilute aqueous solution of sodium carbonate. The part insoluble in the carbonate solution was dissolved in benzene and ligroin was added. Crystals separated and were further purified by recrystallization from alcohol, being deposited as glistening, brownish-yellow needles, melting at 156°. Analysis of this compound showed it to be *paranitrophenylcamphoformeneamine*.

Analysis:

I. 0.1737 gram substance gave 14.8 cc. N at 761 mm. and 19.5°.

II. 0.1108 gram substance gave 0.2772 gram CO₂ and 0.0665 gram H₂O.

	Calculated for	I.	Found.	II.
	$\begin{array}{c} \text{C}_6\text{H}_4 \begin{cases} \text{C}=\text{CH} \\ \\ \text{CO} \end{cases} \begin{cases} \\ \text{NHC}_6\text{H}_4\text{NO}_2 \end{cases} \\ \text{(1)} \qquad \qquad \text{(4)} \end{array}$			
C	68.00			68.23
H	6.66			6.66
N	9.33	9.61		

With alcoholic ferric chloride no color reaction is obtained.

On acidification of the sodium carbonate solution mentioned above with dilute hydrochloric acid, camphoroxalic acid is deposited.

4. *Orthoaminophenol*.—Orthoaminophenol hydrochloride (5.8 grams = 2 mol.) and camphoroxalic acid (4.5 grams = 1 mol.) were heated in alcoholic solution until crystals began to form. These were purified by recrystallization from ethyl acetate, being deposited in well-defined yellow crystals belonging to the monoclinic system and melting at 159°.5. Analysis of this compound showed it to be the lactone of *orthohydroxyphenylcamphoformeneaminicarboxylic acid*.

Analysis:

I. 0.1277 gram substance gave 0.0772 gram H_2O and 0.3413 gram CO_2 .

II. 0.1871 gram substance gave 8.2 cc. N at 750 mm. and 20° .

Calculated for			
$C_6H_{14} \begin{array}{c} \diagup C = C \diagdown \\ \diagdown CO \end{array} \begin{array}{c} COO \\ \\ NH \end{array} \begin{array}{c} O \\ \\ C_6H_4 \end{array} (1)$			
2			
		I.	Found.
			II.
C	72.67	72.89	
H	6.45	6.71	
N	4.72		4.85

The compound is practically insoluble in water, readily soluble in barium hydroxide solution, and slightly soluble in sodium carbonate solution.

When heated to 290° the substance sublimes, forming long, silky, yellow needles which have the same melting point as the original crystals, *i.e.*, $159^\circ.5$. On heating the compound with one molecular proportion of barium oxide at 290° , for forty-five minutes, a tarry mass was formed from which no crystals could be obtained. Some of the compound described above was dissolved in aqueous barium hydroxide solution and boiled for five minutes, then a little alcohol was added and the solution allowed to stand overnight. It was then acidified with dilute hydrochloric acid and crystals separated. After washing them with water and drying, they melted at 155° - 157° , and on recrystallizing the compound once from ethyl acetate the product melted at $159^\circ.5$, showing that this treatment with alkali had caused no change. The substance is, therefore, evidently a lactone.

With alcoholic ferric chloride no color reaction was produced.

5. *Paraminophenol*.—Paraminophenol (5 grams = 2 mol.), camphoroxalic acid (5 grams = 1 mol.), and absolute alcohol (40 cc.) were heated under pressure for two hours, at 105° - 110° . A few crystals had separated on cooling, and a further portion was obtained on concentrating the solution. Recrystallization from alcohol caused the compound to be deposited in light yellow, feathery crystals, melting at 190° and decom-

posing when heated above the melting point. Analysis of this substance showed it to be *paraminophenol parahydroxy phenylcamphoformolaminecarboxylate*.

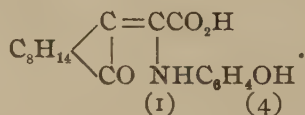
Analysis:

I. 0.1083 gram substance gave 0.2587 gram CO_2 and 0.0708 gram H_2O .

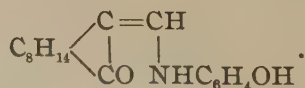
II. 0.1647 gram substance gave 9.1 cc. N at 761 mm. and 23° .

Calculated for			
$\text{C}_8\text{H}_{14}\left\{\begin{array}{l} \text{CHC}(\text{OH})\text{COONH}_2\text{C}_6\text{H}_4\text{OH} \\ \text{CO} \text{ NHC}_6\text{H}_4\text{OH} \end{array}\right.$ (1) (4).			
		I.	Found.
C	65.11	65.14	
H	6.83	7.26	
N	6.34		6.09

When the compound described above is heated for a short time with dilute hydrochloric acid, the crystals become yellow but do not go into solution. Purified by crystallizing from benzene, the compound melts and decomposes at 178° . No analysis was made of this substance, but from the mode of formation and its properties there can hardly be any doubt that it is *parahydroxyphenylcamphoformeneamine-carboxylic acid*,



When this acid is heated above its melting point, carbon dioxide is eliminated and a gum is left which, after solution in benzene, separates in greyish, microscopic crystals, softening at 305° and melting at 314° . From its mode of formation this compound is evidently *parahydroxyphenylcamphoformeneamine*,



6. *Propylamine*.—Propylamine and camphoroxalic acid were mixed in the proportion of 2 molecules of the amine to 1 of the acid and heated in alcoholic solution, so as to prepare a

condensation compound. A gummy mass was formed from which no definite compound could be isolated. Sodium camphoroxalate was also tried with propylamine in alcoholic solution, but with no better results. These experiments were made before my work¹ on secondary amines was completed.

In view of some of the results with aliphatic amines which are described in that paper, there can be little doubt that propylamine and camphoroxalic acid condense to form a liquid compound which could probably be purified by distillation under diminished pressure. Unfortunately there was no time to test this idea.

7. *Metaphenylenediamine*.—Attempts to prepare condensation compounds with this amine and camphoroxalic acid were carried out as follows: The amine hydrochloride (1 mol.), camphoroxalic acid (1 mol.), and potassium hydroxide (2 mol.) were heated under pressure, with absolute alcohol, at 130° for 5 hours. After removing the solution from the potassium chloride formed, it was attempted to purify the crystals separating from the alcohol by using various solvents, but they were contaminated with inorganic matter from which they could not be freed. Consequently they gave no definite melting point and no concordant analytical results.

8. *Paraphenylenediamine*.—The experiments with this compound were made in a similar manner to those with the meta derivative, the results being essentially the same. There is no doubt that, in both cases, a reaction takes place. The compounds which are likely to have been formed are not, however, at present of sufficient importance to me to justify the large expenditure of time and material which would be needed for their isolation, consequently the matter was not pursued further.

TERTIARY AMINES.

9. *Trimethylamine*.—Trimethylamine hydrochloride (4 grams = 1 mol.) was dissolved in absolute methyl alcohol. To this was added potassium hydroxide (2.35 grams = 1

¹ Am. Chem. J., 39, 105 (1908); vide also this Dissertation p. 34.

mol.), also in absolute methyl alcohol solution, to liberate the base. The potassium chloride was separated and to the solution camphoroxalic acid (9.5 grams = 1 mol.) was added. Without further heating the alcohol was evaporated over sulphuric acid in a vacuum desiccator. The resulting compound was purified by crystallization from benzene, being deposited in white, microscopic crystals melting and evolving gas at 139°–140°. With alcoholic ferric chloride a violet color is produced. The compound dissolves in aqueous sodium bicarbonate solution with evolution of gas. Analysis showed the substance to be *trimethylamine camphoroxalate*.

Analysis:

0.1833 gram substance gave 7.9 cc. N at 24°.5 and 771 mm.

	Calculated for $\text{C}_8\text{H}_{14}\text{C}(\text{OH})\text{COONH}(\text{CH}_3)_3$	
	$\text{C}_8\text{H}_{14}\text{C}(\text{OH})\text{CO}$	
N	4.95	Found. 4.77

When the preceding compound is heated above its melting point a gum is formed from which it was impossible to isolate a crystalline derivative.

10. *Triethylamine*.—Triethylamine hydrochloride (2 grams = 1 mol.), camphoroxalic acid (3.3 grams = 1. mol.), and potassium hydroxide (0.8 gram = 1 mol.) were mixed and heated in absolute ethyl alcohol. A precipitate of potassium chloride was formed and was separated from the solution, which was then concentrated. The resulting solid was dissolved in benzene and ligroin added. On standing, crystals separated. These were recrystallized several times from benzene, being deposited in small, white needles melting at 102°–103°. With alcoholic ferric chloride, a violet color is produced. The compound dissolves in aqueous sodium carbonate solution with the evolution of gas. As the yield was small, the reaction was repeated under conditions similar to those with trimethylamine, whereupon the yield was very good. Analysis of this compound showed it to be *triethylamine camphoroxalate*.

Analysis:

0.1702 gram substance gave 6.6 cc. N at 23°.5 and 767 mm..

		Calculated for	
		$\text{C}_8\text{H}_{14}\text{C}:\text{C}(\text{OH})\text{COONH}(\text{C}_2\text{H}_5)_3$	
		CO	
N		4.31	Found.
			4.27

When this compound is heated above its melting point a gummy mass is formed which, when dissolved in ethyl acetate, deposits crystals, but these could not be obtained with a definite melting point, nor could concordant analyses of them be made.

II. *Quinine*.—Quinine (5 grams = 1 mol.) and camphoroxalic acid (4 grams = 1 mol.) were dissolved in benzene. The solution was then allowed to remain at the ordinary temperature for 24 hours. At the end of this time the crystals had separated. These were purified by crystallization from ether, being deposited as white, microscopic crystals melting and evolving gas at 160°–161°. With alcoholic ferric chloride solution a violet color is produced. Analysis showed the compound to be *quinine camphoroxalate*.

Analysis:

I. 0.1403 gram substance gave 0.3605 gram CO_2 and 0.0951 gram H_2O .

II. 0.2028 gram substance gave 9.2 cc. N at 25°.5 and 755 mm.

		Calculated for		
		$\text{C}_8\text{H}_{14}\text{C}:\text{C}(\text{OH})\text{COONHC}_{20}\text{H}_{24}\text{O}_2\text{N}$		
		CO		
		I.	Found.	II.
C	70.02	70.07		
H	7.35	7.53		
N	5.12			4.88

When this salt is heated above its melting point a gum is formed, from which no crystals could be obtained. This gum was treated with an aqueous sodium carbonate solution and extracted with ether. Free quinine was isolated from the ethereal solution and, on acidifying the sodium carbonate solution with dilute hydrochloric acid, camphoroxalic acid separated.

12. *Strychnine*.—Strychnine (5 grams = 1 mol.) and camphoroxalic acid (3.4 grams = 1 mol.) were dissolved in benzene and allowed to stand at room temperature for 18 hours. Crystals were formed and these were purified by recrystallization from ethyl acetate, being deposited as small, white needles melting and evolving gas at 214° – 215° . With alcoholic ferric chloride solution a violet color is produced. Analysis showed this compound to be *strychnine camphoroxalate* and that it crystallizes with 0.5 molecule of ethyl acetate.

Analysis:

I. 0.2420 gram substance gave 0.6147 gram CO_2 and 0.1556 gram H_2O .

II. 0.1884 gram substance gave 7.8 cc. N at $23^{\circ}.5$ and 763 mm.

III. 0.7691 gram substance lost 0.0513 gram on heating at 104° .

		Calculated for		Found.	
		C ₈ H ₁₄ $\begin{matrix} \diagup \text{C} : \text{C}(\text{OH})\text{COONH} \\ \diagdown \text{CO} \end{matrix}$ NO ₂ H ₂₂ C ₂₁		I.	
		C ₈ H ₁₄ $\begin{matrix} \diagup \text{C} : \text{C}(\text{OH})\text{COONH} \\ \diagdown \text{CO} \end{matrix}$ NO ₂ H ₂₂ C ₂₁		II.	
		+ 0.5 CH ₃ COOC ₂ H ₅ .			
C	70.91	69.10	69.27		
H	6.85	7.18	7.14		
N	5.02	4.75		4.62	
		Calculated for	Found.		
		0.5 CH ₃ COOC ₂ H ₅ .	III.		
		6.79	6.67		

When the preceding compound is heated above its melting point the odor of camphor is quite noticeable on opening the tube. After removal of the camphor a gum is left from which no crystalline derivative could be isolated.

13. *Brucine*.—With brucine and camphoroxalic acid it was attempted to obtain two isomeric compounds, and with this end in view the reaction was carried out as follows:

Brucine (2.5 grams = 0.5 mol.) was dissolved in hot benzene. To this camphoroxalic acid (2.8 grams = 1 mol.) was added. The solution was allowed to cool and crystals were soon deposited. These were filtered off and to the solution a second quantity of brucine (2.5 grams = 0.5 mol.) was added,

the liquid being heated to dissolve the brucine. On cooling, crystals were formed. These were separated and were found to be identical with the first portion. The compound was purified by recrystallization from alcohol, being deposited in small, glistening, white plates melting and evolving gas at 235° – 236° . The substance gives a violet color with alcoholic ferric chloride solution. Analysis of the compound proved it to be *brucine camphoroxalate*.

Analysis:

0.1822 gram substance gave 7.7 cc. N at $24^{\circ}.5$ and 764 mm.

Calculated for		
$C_{23}H_{14} \begin{matrix} \diagup C:O(OH)COONHC_{23}H_{26}O_4N \\ \diagdown CO \end{matrix}$		
N	4.54	Found. 4.63

This shows that brucine, as well as quinine and strychnine, readily forms salts with camphoroxalic acid and that, under the conditions employed, no isomeric derivatives are produced. This matter will receive further attention subsequently.

When the brucine salt is heated above its melting point, water and carbon dioxide are given off and the odor of camphor is very pronounced. A gummy mass is left in the tube, from which no crystals could be isolated by the use of ordinary solvents. The gum was treated, finally, with dilute sodium carbonate solution and extracted with ether. A very small amount of material was dissolved in the ether. Some of it, which did not dissolve in the carbonate solution, was recrystallized and found to be impure brucine. On acidifying the carbonate solution with dilute hydrochloric acid a small amount of camphoroxalic acid separated. Evidently the salt had decomposed under the conditions of the heating and subsequent treatment.

14. *Benzalaniline*.—Benzalaniline (4 grams = 1 mol.), camphoroxalic acid (5 grams = 1 mol.), and absolute alcohol (30 cc.) were heated under pressure at 120° , for two hours. On evaporating the alcohol a gummy mass was left, but when this was dissolved in benzene and ligroin was added, crystals

separated. These were purified by recrystallization from benzene, separating as yellow, microscopic crystals melting at 174° . Analysis showed this compound to be *phenylcamphorformeneaminecarboxylic acid*.

Analysis:

I. 0.1035 gram substance gave 0.2740 gram CO_2 and 0.0734 gram H_2O .

II. 0.1807 gram substance gave 7.8 cc. N at 22° and 762 mm.

Calculated for		Found.	
		I.	II.
$\text{C}_6\text{H}_5 \begin{cases} \text{C}=\text{CCOOH} \\ \text{CO} \text{ NHC}_6\text{H}_5 \end{cases}$			
C	72.24	72.20	
H	7.02	7.87	
N	4.68		4.79

This compound was found to be identical with that prepared by Bishop Tingle¹ from aniline and camphoroxalic acid. Comparative melting points were made on the compound from benzalaniline and aniline by using three capillary tubes, containing, respectively, the compound from benzalaniline, that from aniline, and a mixture of the two. The three tubes were heated at once and the substance in each melted at the same point, namely, 174° . As has been pointed out before, such comparisons are necessary to establish the identity of many compounds of this series, because the melting point depends greatly on the rapidity with which the substances are heated. It is evident that, under the conditions employed, benzalaniline is hydrolyzed to its constituents, the aniline combining with the camphoroxalic acid and the benzaldehyde remaining in the free state. The bearing of this fact on the general course of the condensation of camphoroxalic acid with bases is pointed out in the theoretical portion of this dissertation.

Another attempt to prepare a condensation product from camphoroxalic acid and benzalaniline was made as follows:

Benzalaniline (5.5 grams = 1.5 mol.), sodium camphoroxalate (5 grams = 1 mol.), and 40 cc. of anhydrous benzene,

¹ Am. Chem. J., **21**, 238 (1899).

which had been dried over sodium, were heated under pressure for four hours, at 105° – 108° . When the benzene was evaporated in a vacuum desiccator over sulphuric acid, a gummy mass was left. As no crystals could be separated by dissolving the product in ordinary solvents, it was dissolved in alcohol and acidified with dilute acetic acid. After being freed from the sodium acetate, the solution was concentrated and a gum was formed. This was dissolved in benzene and sodium carbonate added. On acidifying the sodium carbonate solution with dilute hydrochloric acid, a yellow precipitate was deposited. This was purified by recrystallizing from benzene and was found to be identical with the compound obtained in the former experiment.

15. *Piperine*.—Piperine (7.1 grams = 1 mol.), camphoroxalic acid (6.7 grams = 1 mol.), and benzene (60 cc.) were heated under pressure at 165° for five hours. Some crystals had separated when the bomb was opened.

These were recrystallized from alcohol and were deposited in light yellow needles, softening at 210° and melting at 217° . The color, form, and melting point of these crystals correspond exactly with those of piperic acid.

On concentrating the solution from the bomb, crystals were deposited. These were recrystallized from alcohol and were found to be unchanged piperine.

An analysis for nitrogen was made with the compound before its nature was known but, of course, none was found.

The piperic acid was formed in very small quantity. Its production is doubtless due to traces of moisture in the materials and vessel used in the experiment.

16. *Tribenzylamine*.—Tribenzylamine and camphoroxalic acid were heated, in alcoholic solution, on the water bath, and a gum was formed from which I was unable to isolate a crystalline compound with a definite melting point. A semicrystalline mass was separated from the gum, but it could not be obtained in a pure condition. On treating this with sodium carbonate and extracting with ether, free tribenzylamine was obtained from the ethereal solution. The

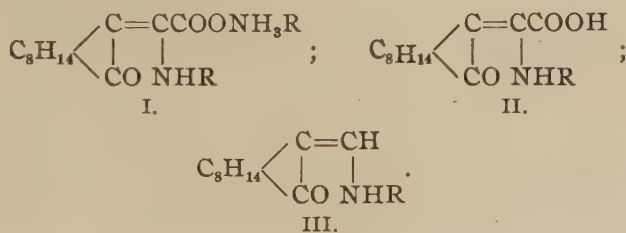
sodium bicarbonate solution was acidified with dilute hydrochloric acid. This causes a separation of camphoroxalic acid and showed that the treatment with carbonate had decomposed the semi-crystalline mass. The latter must, therefore, have consisted of *tribenzylamine camphoroxalate*.

17. *Tetraethylammonium Hydroxide*. — Tetraethylammonium hydroxide, 10 per cent aqueous solution, and camphoroxalic acid were mixed in 95 per cent alcohol and heated for a short time. The alcohol was allowed to evaporate spontaneously and the residue was crystallized from benzene, being deposited in glistening white needles. These give a violet color with ferric chloride solution. Attempts were made to analyze this compound, but it decomposes so easily that no concordant results could be obtained. It is, doubtless, *tetraethylammonium camphoroxalate*.

PART II.

Study of the Action of Certain Secondary Amines on Camphoroxalic Acid.

In the course of an investigation by Bishop Tingle and Hoffman,¹ it was found that dimethylamine and diethylamine condense with camphoroxalic acid. The products consist, empirically, of 1 molecule of acid + 2 molecules of base, no water being eliminated. Compounds of secondary bases and ketones or enols had not, hitherto, been prepared; consequently the bodies in question possessed a special interest and made me anxious to elucidate the subject more fully. I also wished to throw some light on the constitution of these substances. On comparing them with the condensation compounds of camphoroxalic acid and primary amines, it is seen that their constitution presents a decided peculiarity. Bishop Tingle and his co-workers have shown² that this acid condenses with primary amines, forming derivatives belonging to one of the three following types:



From what has been said above, it will be apparent that the compounds from secondary amines resemble, in general, type I., but differ from it by containing, in addition, the elements of water. It has been shown in earlier papers that in all probability substances of type I. are formed by the addition of the primary amine to the double linkage and also, in some

¹ Am. Chem. J., **34**, 217 (1905).

² *Loc. cit.*

cases, to the carboxyl group, giving the intermediate compound,



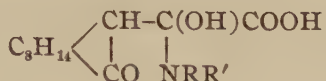
As a rule, these intermediate bodies are unstable and readily eliminate water, passing into substances of type I.

Some of them, however, are quite stable. A number of these have been described in previous papers by Bishop Tingle and his co-workers,¹ and I myself have obtained two others, from ethylenediamine and paraminophenol, respectively, in the course of some work on primary amines and camphor-oxalic acid. The results of this investigation are given in the first part of this dissertation. On account of the presence of the extra molecule of water in these substances, they have received the name of *camphoformolamine derivatives*.

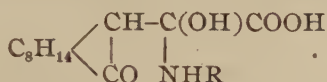
With regard to the compounds of the secondary amines and camphoroxalic acid, it is not unnatural to suppose that they might be representatives of this intermediate, additive form. There are two reasons which, at present, lead me to reject this view of their constitution. The first and most important is based on the fact that they give an intense violet coloration with ferric chloride and alcohol. Compounds of types I. and II., from the primary amines, and also the addition products of these amines which have just been referred to, give no color with this reagent, whereas camphoroxalic acid itself gives a deep red color. It is well known that these pronounced colorations are characteristic of the group C:COH, consequently, although the derivatives of the secondary amines must, no doubt, differ from the parent acid, yet they must contain the group in question. A second consideration leading towards the same conclusion is this: Secondary aliphatic amines are, in general, more strongly basic than the corresponding primary compounds. Other things being equal, the readiness with which water is eliminated from a compound is decreased by the presence of negative groups in the molecule. Consequently, in so

¹ *Vide p. 7.*

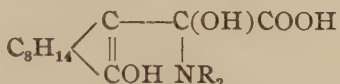
far as this reasoning is applicable to the case in question, the compound



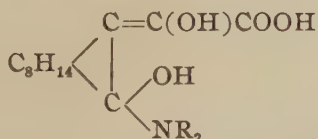
should eliminate the elements of water *more* readily than a substance with the constitution



Actually, of course, the exact opposite is found to be the case. These considerations lead me, therefore, to the formula



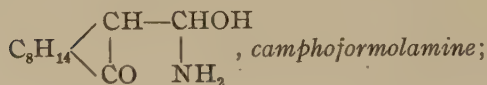
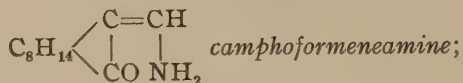
as the best expression of the constitution of the compounds of camphoroxalic acid and the secondary amines. As in the case of almost all the derivatives of this acid which have been studied, it is based upon the assumption that the primary point of attack is the C:COH group. The grounds on which this belief is based have been fully discussed by Bishop Tingle and Robinson,¹ and need not be repeated here. Should subsequent work ever show them to be invalid, the only change which would be involved in the formulas given above would be the representation of the nitrogen atom as being linked to the ketonic instead of to the enolic carbon atom, thus



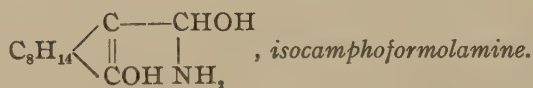
The question at once arises as to the designation of these compounds. Until their constitution is definitely established, it appears to me that the simplest plan is to term them *iso-*

¹ Am. Chem. J., **36**, 223 (1906).

camphoformolamine derivatives; we have, then, three series of substances derived from the following complexes, *viz.*:



and



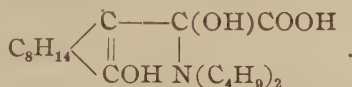
When these isocamphoformolaminocarboxylic acids, or their salts, are heated above their melting points, water and carbon dioxide are evolved, and products are obtained which are without action on ferric chloride and which resemble closely, in general properties, the compounds prepared, under corresponding conditions, from the condensation products of camphoroxalic acid and primary amines. They have, therefore, been formulated, in a manner similar to these latter, as alkyl or aryl derivatives of type III. given above. The secondary amines resemble the primary ones in that the ability of any individual one of them to form derivatives of both the isocamphoformolamine type or of type III. differs for each amine. This point is discussed more fully elsewhere in the present dissertation, *vide* p. 7.

The first object of the investigation described in the following pages was to apply the reaction discovered by Bishop Tingle and Hoffman to a number of other secondary amines. This has been done with a very considerable measure of success. The second object which I had in view was to obtain more experimental evidence for the formula which I have assigned to the compounds in question. This part of the work has been seriously interfered with by lack of the needed material which, though ordered from the authorities of the Johns Hopkins University early in June 1906, did not reach me until

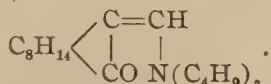
February 1907. There was nothing in the nature of the supplies themselves to excuse this delay,

The compounds named below have been studied. The nomenclature employed for the designation of the products of the reactions has been fully elucidated in the article by Tingle and Hoffman.¹

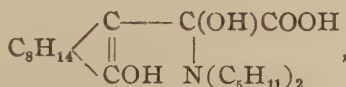
1. *Diisobutylamine* and camphoroxalic acid give *diisobutylisocamphoformolaminocarboxylic acid*,



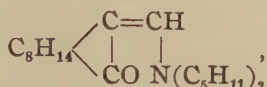
When this is heated above its melting point it forms *diisobutylcamphoformeneamine*,



2. *Diamylamine* gives *diamylisocamphoformolaminocarboxylic acid*,

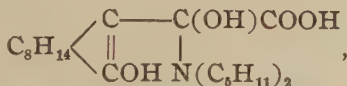


which forms *diamylcamphoformeneamine*,

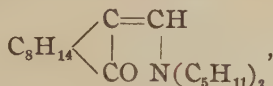


when heated above its melting point.

3. *Diisoamylamine* gives *diisoamylisocamphoformolaminocarboxylic acid*,



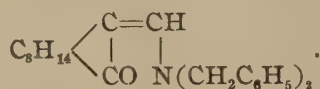
which is converted into *diisoamylcamphoformeneamine*,



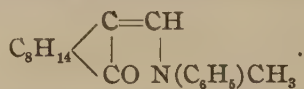
when heated above its melting point.

¹ *Loc cit.*

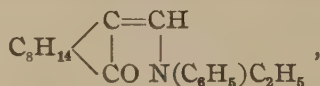
4. *Dibenzylamine* and camphoroxalic acid react with greater difficulty than the amines mentioned above. The product is *dibenzylcamphoformeneamine*,



5. *Methylaniline* and camphoroxalic acid also react with some difficulty, forming *phenylmethylcamphoformeneamine*,

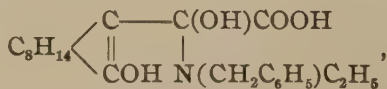


6. *Ethylaniline* gives *phenylethylcamphoformeneamine*,

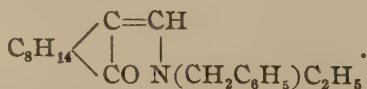


a viscous liquid.

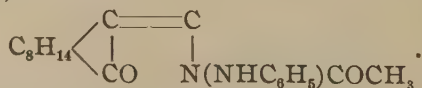
7. *Benzylethylamine* gives *benzylethylisocamphoformolamine-carboxylic acid*,



which, when heated above its melting point, is changed to *benzylethylcamphoformeneamine*,



8. *Acetylphenylhydrazine* gives *acetylphenylaminecamphoformeneamine*,

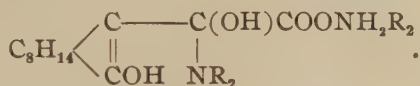


The conduct of the following acyl secondary bases towards camphoroxalic acid was also studied:

Paranitrobenzoylparaminophenol, *diparanitrobenzoylparaminophenol*, *metanitrobenzoylparaminophenol*, *dimetanitrobenzoylparaminophenol*, *paranitrobenzoylorthoaminophenol*, *diparanitrobenzoylorthoaminophenol*, *metanitrobenzoylorthoaminophenol*, *dimeta-*

nitrobenzoylorthoaminophenol, *phenylsulphoneparaminophenol*, *phenylsulphoneorthoaminophenol*, *diphenylsulphoneorthoaminophenol*, and *paracetoaminophenol*. No single one of these acyl derivatives could, however, be induced to undergo reaction. Besides these I also investigated the behavior of *benzoylphenylhydrazine*, *benzylphenylhydrazine*, *benzylmethylamine*, *benzylaniline*, *phenylhydrazine-p-sulphonic acid*, *phenyl-β-naphthylamine*, and symmetrical *phenylmethylhydrazine*. These compounds likewise failed to react.

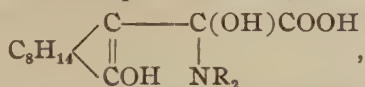
The preceding results permit of some rather interesting conclusions being drawn. In the case of the dimethyl- and diethylamine *two molecules* combine with *one* of camphoroxalic acid, forming a salt of the isoformolaminic acid,



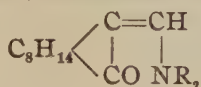
The remaining *aliphatic amines* which I have tried yield directly the *free acid* corresponding to the above salt. Bishop Tingle and Hoffman¹ were unable to prepare, from the salts of the dimethyl and diethyl compounds, the corresponding free acids. According to the system of nomenclature suggested by me, their two compounds should be termed *isocamphoformolamine*, not *camphoformolamine*, derivatives.

Evidently, therefore, the entrance of the more strongly basic, higher alkyl amine radical into the molecule of camphoroxalic acid has so weakened its acidic properties as to render it essentially a neutral body, incapable of salt formation. The gradation is a very interesting and delicate one.

In the case of the alkyl aniline derivatives which are, of course, feebler bases than the aliphatic amines, the acid type,



is rendered too unstable to be isolated, carbon dioxide and water are evolved spontaneously, and neutral products of the formula



¹ *Loc. cit.*

are formed. The same is true of the condensation products of acetylphenylhydrazine and of dibenzylamine, which react like the alkyl anilines, whereas ethylbenzylamine behaves exactly like the aliphatic amines.

In the case of benzylaniline and of β -naphthylaniline, it is evident that the basic properties are too feeble to permit of condensation taking place under the most favorable conditions which I was able to employ. I do not think that my results lend any definite support to a theory of spatial hindrance, but it would be difficult to obtain a clearer or more delicate representation of the changes in the nature of the amines.

The condensation compound from acetylphenylhydrazine deserves a few words of separate treatment, not only because I believe that it is the *first* condensation product which has ever been obtained from this amine, but also because I think that it is the first acylated amine which has been induced to react with a ketonic or enolic compound. I have made a number of experiments to elucidate its constitution more fully. Although it apparently undergoes hydrolysis rather readily, it is difficult to purify the resulting compound unless the experimental conditions under which it is formed are regulated very carefully. The work in this connection will be continued by Professor J. Bishop Tingle.

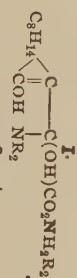
The failure to obtain a similar condensation compound from camphoroxalic acid and benzoylphenylhydrazine is, no doubt, to be ascribed to the more strongly negative nature of the benzoyl, as compared with the acetyl, group.

Of the remaining acylated amines (acylated aminophenols) which have been investigated, none of them showed any signs of a tendency to react with camphoroxalic acid.

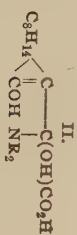
At present it is unnecessary to discuss further these negative results, except to point out that the substances in question, if they exhibit basic properties at all, do so to an extremely slight degree. Their behavior confirms, therefore, the observations and conclusions made by me and also by Bishop Tingle and his co-workers on the amine derivatives of camphoroxalic acid.

Secondary amines.

1. $\text{NH}(\text{CH}_3)_2$
2. $\text{NH}(\text{C}_2\text{H}_5)_2$
3. $\text{NH}(\text{C}_4\text{H}_9)_2$ *iso*
4. $\text{NH}(\text{C}_6\text{H}_{11})_2$
5. $\text{NH}(\text{C}_5\text{H}_{11})_2$ *iso*
6. $\text{NH}(\text{CH}_2\text{C}_2\text{H}_5)_2$
7. $\text{C}_6\text{H}_5\text{NHCH}_3$
8. $\text{C}_6\text{H}_5\text{NHC}_2\text{H}_5$
9. $\text{C}_6\text{H}_5\text{CH}_2\text{NHC}_2\text{H}_5$
10. $\text{CH}_3\text{CONHNHC}_6\text{H}_5$
11. $\text{OC}(\text{NHCH}_3)_2$
12. $\text{C}_6\text{H}_5\text{C}(\text{NH}_2)_2\text{NH}$

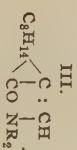


137°.5*
139°.5*

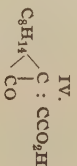


....

180°
160°
156°



163°*
153°*
73°-74°
43°
40°
152°
126°



boils 285° (110 mm.)

158°

....

Yields compound $\text{C}_{19}\text{H}_{24}\text{O}_4\text{N}_2$ 184°*

....

104°-105°*

The foregoing table gives the type formulas and melting points of all the compounds of camphoroxalic acid and secondary amines which have been prepared hitherto. Those described before the appearance of this dissertation are marked.* The derivative of symmetrical dimethylcarbamide is included, although it is a derivative of a primary amine, because the parent substance is a secondary amine. Benzamidine may be regarded as being a secondary amine and, therefore, its derivative has also been given.

EXPERIMENTAL.

1. *Diisobutylamine.*

Diisobutylamine (2.9 grams = 1 molecule) and camphoroxalic acid (5 grams = 1 molecule) were dissolved in absolute ethyl alcohol and heated on the water bath for fifteen minutes. On cooling, crystals were deposited. These were purified by recrystallization from ethyl acetate, from which they separate in glistening, white needles, melting at 179° – 180° with evolution of gas. With alcoholic ferric chloride the violet color, characteristic of the enolic grouping, is produced. Analysis of this compound showed it to be *diisobutylisocamphoformolamine-carboxylic acid*.

Analysis:

0.2078 gram substance gave 7.4 cc. N at 780 mm. and 21° .

	Calculated for	
	$\begin{array}{c} \text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C} \text{---} \text{CCO}_2\text{H} \\ \diagdown \parallel \text{COH} \end{array} \text{N}(\text{C}_4\text{H}_9)_2 \end{array}$	
N	3.97	Found.
		4.08

When this substance is heated above its melting point, water and carbon dioxide are eliminated and a gum is left. This is purified by dissolving it in acetone; it deposited in white plates, melting at 73° – 74° . With alcoholic ferric chloride no color reaction is produced. Analysis showed this compound to be *diisobutylcamphoformeneamine*.

Analysis:

0.1043 gram substance gave 4.4 cc. N at 760 mm. and 24° .

	Calculated for	
	$\text{C}_8\text{H}_{14} \begin{cases} \text{C}=\text{CH} \\ \text{CO} \end{cases} \text{N}(\text{C}_4\text{H}_9)_2$	Found.
N	4.81	4.61

2. Diamylamine.

Diamylamine (7 grams = 2 mol.) and camphoroxalic acid (5 grams = 1 mol.) were heated in absolute alcoholic solution on the water bath. On cooling, crystals were deposited which were found to be readily soluble in methyl and ethyl alcohols, ethyl acetate, acetone, ether, and benzene. The compound was purified by recrystallizing from acetone. It separated in white, microscopic crystals melting at 160°. A violet color is produced by dissolving it in alcohol and adding ferric chloride. The compound dissolves in sodium bicarbonate solution with evolution of gas. Analysis showed the substance to be *diamylisocamphoformolaminecarboxylic acid*.

Analysis:

I. 0.1713 gram substance gave 0.4360 gram CO_2 and 0.1644 gram H_2O .

II. 0.2912 gram substance gave 9.4 cc. N at 762 mm. and 24°.

	Calculated for		Found.
	$\text{C}_8\text{H}_{14} \begin{cases} \text{C}—\text{C}(\text{OH})\text{CO}_2\text{H} \\ \text{COH} \end{cases} \text{N}(\text{C}_5\text{H}_{11})_2$	I.	II.
C	69.23	69.41	. .
H	10.30	10.66	. .
N	3.68	. .	3.54

Diamylamine and camphoroxalic acid were also brought together under the following conditions: Camphoroxalic acid (2 grams = 1 mol.) was dissolved in alcohol and with this was mixed an amount of potassium hydroxide nearly sufficient to neutralize it. Diamylamine (1.4 grams = 1 mol.) was now added and the solution concentrated. After this heating, the liquid was rendered barely acid with dilute hydrochloric acid and the crystals which formed were recrystallized from acetone. The purified product was found to be identical with the compound described above.

When this substance is heated above its melting point, in a tube connected with a vessel containing baryta water, carbon

dioxide is given off, as is shown by the formation of barium carbonate. Water is also eliminated.

The resulting gummy material was treated with benzene and ligroin, and crystals were formed. Recrystallization from acetone and then from ethyl acetate resulted in the deposition of white plates melting at 43°. It was difficult to free these crystals from gum, although they were subjected to the action of various solvents a number of times. Analysis indicated that the compound was *diamylcamphoformeneamine*.

Analysis:

0.1715 gram substance gave 6.4 cc. N at 753 mm. and 24°

Calculated for		Found.
$\text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C}=\text{CH} \\ \diagdown \text{CO} \text{ N}(\text{C}_6\text{H}_{11})_2 \end{array}$		
N	4.40	4.04

3. Diisoamylamine.

Diisoamylamine (3.2 grams = 2 mol.) and camphoroxalic acid (2.5 grams = 1 mol.) were dissolved in alcohol and heated till nearly all the solvent was evaporated. Ligroin was then added to the mixture and, on standing, crystals separated. These were purified by recrystallization from acetone, being deposited in white, microscopic crystals melting at 156°. In alcoholic solution a violet color is produced with ferric chloride. The compound dissolves in aqueous sodium bicarbonate solution with evolution of gas. Analysis showed it to be *diisoamylisocamphoformolaminecarboxylic acid*.

Analysis

0.1917 gram substance gave 6.4 cc. N at 760 mm. and 25°.

	Calculated for	
	$\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C}=\text{C}(\text{OH})\text{CO}_2\text{H} \\ \diagdown \text{COH} \text{ N}(\text{C}_6\text{H}_{11})_2 \end{array}$	Found.
N	3.68	3.62

When the above compound is heated above its melting point, water and carbon dioxide are eliminated and a gummy mass is left in the tube. This material was purified by recrystallizing from ethyl acetate, being deposited in whitish, rather ill-de-

finer crystals melting at 40° . With alcoholic ferric chloride there is no color reaction. Analysis showed this substance to be *diisoamylcamphorformeneamine*.

Analysis:

0.1400 gram substance gave 5.4 cc. N at 757 mm. and 25° .

Calculated for		Found.
$\begin{array}{c} \text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C}=\text{CH} \\ \diagdown \text{CO} \end{array} \text{N}(\text{C}_6\text{H}_{11})_2 \end{array}$		
N	4.40	4.17

4. *Dibenzylamine*.

Dibenzylamine (4 grams = 1 mol.), camphoroxalic acid (4.6 grams = 1 mol.), and absolute ethyl alcohol (30 cc.) were heated under pressure, at 130° , for 3 hours, the air in the tube being replaced with illuminating gas. Pressure was noticed in the tube when it was opened and on agitating the solution crystals separated. These were purified by recrystallizing from ethyl acetate and then from alcohol. The compound is deposited in small, glistening, white crystals, melting at 152° .

With alcoholic ferric chloride no color is produced.

Analysis showed this compound to be *dibenzylcamphorformeneamine*. Analysis:

I. 0.1531 gram substance gave 0.4690 gram CO_2 and 0.1182 gram H_2O .

II. 0.1989 gram substance gave 7.0 cc. N at 763 mm. and 25° .

Calculated for		Found.	
$\begin{array}{c} \text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C}=\text{CH} \\ \diagdown \text{CO} \end{array} \text{N}(\text{CH}_2\text{C}_6\text{H}_5)_2 \end{array}$		I.	II.
C	83.56	83.54	. .
H	8.07	8.57	. .
N	3.90	. .	3.83

5. *Methylaniline*.

Methylaniline (4.3 grams = 1 mol.), camphoroxalic acid (9 grams = 1 mol.), and benzene (50 cc.) were heated under pressure, at 120° , for 5 hours. Upon evaporating the excess of benzene a gummy mass remained, from which no crystals could be separated by the use of various solvents, the product always

depositing from solution as a gum. This gum was, therefore, treated with an aqueous sodium carbonate solution and then extracted with ether. Upon acidifying the carbonate solution with dilute hydrochloric acid, free camphoroxalic acid was precipitated.

The ether solution, when evaporated, deposited crystals which were purified by recrystallization from ethyl acetate, separating in slightly yellow, tetrahedral forms, melting at 126° . With alcoholic ferric chloride no color is produced. Analysis of this compound showed it to be *phenylmethylcamphoformeneamine*. Analysis:

I. 0.1053 gram substance gave 0.3099 gram CO_2 and 0.0864 gram H_2O .

II. 0.1102 gram substance gave 5.3 cc. N at 770 mm. and 24° .

	Calculated for $\text{C}_8\text{H}_{14}\left\{\begin{array}{l} \text{C}=\text{CH} \\ \\ \text{CO N (C}_6\text{H}_5\text{)CH}_3 \end{array}\right.$	Found.	
		I.	II.
C	80.23	80.26	. .
H	8.61	8.92	. .
N	5.21	. .	5.33

6. Ethylaniline.

Ethylaniline (2.15 grams = 1 mol.), camphoroxalic acid (4 grams = 1 mol.), and benzene (40 cc.) were heated under pressure, at 120° , for 5 hours. About half the benzene was then evaporated and ligroin added to the solution. On standing, a gum was deposited. This was treated with sodium carbonate solution in the manner described in the preceding section, and extracted with ether. When the carbonate solution was acidified with dilute hydrochloric acid, camphoroxalic acid was precipitated.

Upon evaporating the ether solution, a liquid was left and, as it could not be induced to form crystals, it was finally distilled under diminished pressure. Two fractions were obtained. The first, boiling at 140° – 145° (110 mm.), was found to be ethylaniline. The second fraction boiled at 285° (110 mm.) and is a deep yellow, viscous liquid. Analysis showed this to be *phenylethylcamphoformeneamine*. Analysis:

I. 0.2247 gram substance gave 0.6580 gram CO_2 and 0.1804 gram H_2O .

II. 0.2253 gram substance gave 10.4 cc. N at 770 mm. and 24.5° .

	Calculated for $\text{C}_8\text{H}_{14}\left\{\begin{array}{l} \text{C}=\text{CH} \\ \\ \text{CO} \end{array}\right. \text{N}(\text{C}_6\text{H}_5)_2\text{C}_2\text{H}_5$	Found.	
		I.	II.
C	80.50	79.86	. .
H	8.89	8.92	. .
N	4.95	. .	5.10

7. Benzylethylamine.

Benzylethylamine (4.5 grams = 1.5 mols.) and camphoroxalic acid (5 gram = 1 mol.) were mixed and heated in absolute ethyl alcoholic solution on the water bath, for 15 minutes. On cooling, crystals were deposited. These were purified by recrystallizing from ethyl acetate and were deposited in fine, white, flocculent crystals melting at 158° with evolution of gas. With alcoholic ferric chloride solution, a violet color is produced. The compound dissolves in sodium bicarbonate solution with evolution of gas. Analysis showed this substance to be *benzylethylisocamphorolaminecarboxylic acid*. Analysis:

I. 0.1329 gram substance gave 0.3423 gram CO_2 and 0.1007 gram H_2O .

II. 0.1506 gram substance gave 5.5 cc. N at 758 mm. and 24° .

	Calculated for $\text{C}_8\text{H}_{14}\left\{\begin{array}{l} \text{C}-\text{C}(\text{OH})\text{CO}_2\text{H} \\ \quad \\ \text{COH} \quad \text{N}(\text{CH}_2\text{C}_6\text{H}_5)_2\text{C}_2\text{H}_5 \end{array}\right.$	Found.	
		I.	II.
C	70.13	70.24	. .
H	8.13	8.42	. .
N	3.89	. .	3.99

When this compound is heated above its melting point, in a tube connected with a vessel containing baryta water, carbon dioxide is eliminated, as is shown by the formation of barium carbonate in the liquid. Water also is given off. After cooling, a yellow gum was left. As no crystals could be separated by use of ordinary solvents, this gum was treated with sodium carbonate and the solution extracted with ether. A yellow oil was left after evaporating the ether. This solidified on standing.

It was redissolved in alcohol and from this solution white crystals are deposited which melt at 57° . With ferric chloride and alcohol no color reaction is produced. Analysis showed the compound to be *benzylethylcamphoformeneamine*.

Analysis:

0.1867 gram substance gave 7.7 cc. N at 760 mm. and 23° .

N	Calculated for	Found.
	$\begin{array}{c} \text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C}=\text{CH} \\ \diagdown \text{CO} \end{array} \text{N}(\text{CH}_2\text{C}_6\text{H}_5)_2 \\ \text{4.72} \end{array}$	4.54

8. Acetylphenylhydrazine.

Acetylphenylhydrazine (4.5 grams = 1 mol.), camphor-oxalic acid (6.75 grams = 1 mol.), and benzene (30 cc.) were heated under pressure, at 140° – 145° , for 14 hours. A considerable evolution of gas was noticed when the tube was opened. When the benzene solution was evaporated, a tarry mass was formed from which no crystals could be separated by the use of various solvents; consequently, the tar was treated with sodium carbonate solution. The part insoluble in the carbonate solution was dissolved in benzene, and ligroin was added. On standing for several days crystals were deposited. These were recrystallized from ethyl acetate several times and then from ethyl alcohol, because the last traces of impurity were difficult to remove. The compound was finally deposited from alcohol in white needles melting at 174° . With alcoholic ferric chloride solution no color reaction is produced. Analysis showed it to be *acetylphenylaminecamphoformeneamine*. Analysis:

I. 0.1110 gram substance gave 0.2970 gram CO_2 and 0.0824 gram H_2O .

II. 0.1074 gram substance gave 9.1 cc. N at 758 mm. and 24° .

	Calculated for	Found	
	$\begin{array}{c} \text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C}=\text{CH} \\ \diagdown \text{CO} \end{array} \text{N}(\text{COCH}_3)\text{NHC}_6\text{H}_5 \\ \text{73.07} \\ \text{7.68} \\ \text{8.97} \end{array}$	I.	II.
C	73.07	72.97	. .
H	7.68	8.24	. .
N	8.97	. .	9.24

Some of this compound was heated with potassium hydroxide solution of medium concentration for 3 hours, and then allowed to stand for 40 hours at the room temperature. The solution was now made acid with hydrochloric acid and extracted with ether. The crystals deposited from the ether solution were found to be unchanged material.

A second portion of the substance was then heated with somewhat dilute hydrochloric acid, 2 parts of concentrated acid to 1 part of water, for 3 hours and allowed to stand at the room temperature for 40 hours. The solution was now diluted with water and extracted with ether. From the ether solution, crystals are deposited. They were recrystallized from acetone and came down in glistening, white plates melting at 135° . The compound did not appear to be pure because the melting point was not very sharp, and no concordant analyses could be obtained. Time was lacking for the preparation of larger quantities of this interesting material, but a more complete study of it will be made in the near future.

SECONDARY AMINES WITH WHICH NO CONDENSATION COMPOUNDS WERE FORMED.

The following acyl derivatives of ortho- and paraminophenol: *Paranitrobenzoylparaminophenol*, *diparanitrobenzoylparaminophenol*, *metanitrobenzoylparaminophenol*, *dimetanitrobenzoylparaminophenol*, *paranitrobenzoylorthoaminophenol*, *diparanitrobenzoylorthoaminophenol*, *metanitrobenzoylorthoaminophenol*, *dimetanitrobenzoylorthoaminophenol*, *phenylsulphoneparaminophenol*, *phenylsulphoneorthoaminophenol*, and *diphenylsulphoneorthoaminophenol* were heated under pressure, in benzene solution, with camphoroxalic acid to temperatures varying from 165° to 175° , being maintained at these temperatures for several hours, but in no case was there any reaction.

In a paper which was published about a year ago¹ on "Acyl Derivatives of Ortho- and Paraminophenol," Bishop Tingle and the writer described the preparation and properties of *metanitrobenzoylorthoaminophenol* and stated that we had

¹ Am. Chem. J., **37**, 51 (1907).

prepared it for the first time. Professor Ransom has pointed out to me that he was the first to obtain this compound, as stated in his dissertation.¹

Paracetoaminophenol was also heated under pressure, in benzene solution, with camphoroxalic acid, at 160°, but no reaction took place.

Benzoylphenylhydrazine and camphoroxalic acid were heated, in benzene solution, at 150° under pressure, and a tarry mass was formed. This was treated with sodium carbonate and the insoluble part dissolved in various solvents, but no definite compound could be isolated. On acidifying the sodium carbonate solution with dilute hydrochloric acid, a small amount of camphoroxalic acid separated.

Benzylphenylhydrazine and camphoroxalic acid were heated in benzene solution, at 140°. A gum formed and this was treated in the same manner as described for the gum from benzoylphenylhydrazine, but no definite compound could be obtained.

Benzylmethylamine and camphoroxalic acid were mixed and heated in absolute ethyl alcohol solution for a short time. The alcohol was then evaporated and a gummy mass was formed, from which no definite compound could be separated.

Phenylmethylhydrazine and camphoroxalic acid were mixed and heated for a short time with absolute methyl alcohol. The solvent was evaporated slowly and a gum was left. This was treated with various solvents but no crystals could be separated from the gum. This latter was then treated with sodium carbonate solution and extracted with ether. The ether solution deposited only a resinous mass, from which no definite compound could be isolated. The sodium carbonate solution was acidified with dilute hydrochloric acid and some camphoroxalic acid separated.

Benzylaniline and camphoroxalic acid were mixed and heated, in benzene solution, for an hour and then the benzene evaporated gradually. A viscid liquid was left, from which no definite compound could be separated. This gum was treated with

¹ Univ. of Chicago, 1900, p. 28.

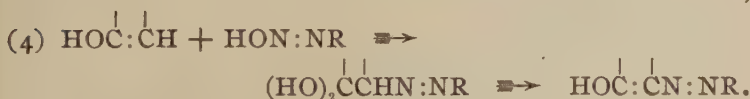
sodium carbonate and extracted with ether. Benzylaniline was left on evaporating the ether, and from the sodium carbonate solution camphoroxalic acid separated on acidifying the liquid with dilute hydrochloric acid.

Phenyl-β-naphthylamine and camphoroxalic acid were heated in benzene solution, under pressure, at 160°, but no reaction whatever took place.

Paraphenylhydrazinesulphonic acid and camphoroxalic acid were heated under pressure, in benzene solution, at 175°, but the two compounds were recovered unchanged.

The action of *benzalaniline* on camphoroxalic acid is described earlier in this dissertation, vide p. 25.

Some months after the completion of the work described in the preceding pages, I noticed a paper by O. Dimroth¹ on the interaction of *p*-nitrobenzenediazonium hydroxide and certain ketonic and enolic compounds. After a general discussion of the subject, he suggests the following four equations as representing the possible modes of condensation of these substances:



The last equation is correct as given here, but is erroneous in Dimroth's paper. Dimroth rejects equation (1) because he failed to obtain condensations with the ketonic compounds which he investigated. The second equation is also discarded because enolic acetyldibenzoylmethane and enolic ethyl diacetylsuccinate, which contain no CH group, condense readily

¹ Ber. d. chem. Ges., 40, 2404 (1907).

with the diazonium derivative. As between the third and fourth equations, he favors the latter, because only "enols (phenols), but not their ethers or esters, are reactive" in this sense. He states, however, that it is impossible to decide between the two equations until additive compounds of the one or other kind have been prepared and investigated. Dimroth has evidently failed to acquaint himself with the literature on the subject of his investigation, otherwise he would not have overlooked the fact that Bishop Tingle alone, and also in conjunction with Alfred Tingle, W. E. Hoffman, Jr., and C. J. Robinson, has described a number of such *addition* compounds, which are termed *camphoformolamine* derivatives, the most interesting being those of camphoroxalic acid with hydroxylamine and *p*-bromophenylhydrazine, respectively. These are, of course, apart altogether from the additive compounds mentioned for the first time in the present dissertation. The description of the substances in question, together with full discussions of their constitution and of the bearing which they have on the enolic-ketonic question, are to be found in some eight or ten papers, published at intervals during the past 10 years, chiefly in the AMERICAN CHEMICAL JOURNAL. The question is dealt with most fully, perhaps, in the paper by Bishop Tingle and Robinson.¹ If Dimroth's reasoning is valid, it follows that the question under consideration was settled some years ago by Bishop Tingle and his colleagues, who regard the fourth of the above equations as the correct representation of the reactions in question, and who have, therefore, always formulated their results in accordance with it. It is a pleasure to receive Dimroth's adhesion to the views which Bishop Tingle first recorded many years ago, and although his experimental results are in no way decisive for either method of formulation, yet I welcome them because, in so far as they go, they support the work of Bishop Tingle and me.

I desire, in conclusion, to express my grateful thanks to the Trustees of the Warren Research Fund of the American Academy of Arts and Sciences for a grant in aid of the purchase of some of the chemicals employed in this investigation.

¹ Am. Chem. J., **36**, 223 (1906).

PART III.

Acyl Derivatives of Ortho- and Paraminophenol.

INTRODUCTORY.

In the course of an investigation of condensation compounds of amines and camphoroxalic acid, I found it necessary to prepare relatively large quantities of ortho- and paraminophenol.

Arising out of this work I found it desirable to clear up some doubtful points regarding the preparation of ortho- and paraminophenol by Morse's method.¹ This was done successfully and I thought it well to extend my work on the condensation products of secondary amines with camphoroxalic acid so as to include a study of the behavior of this acid toward the acyl derivatives of the aminophenols, which are, of course, secondary bases, *vide* p. 34. This led me to prepare many new compounds belonging to the class in question and to correct a number of errors which have been made in the description of those already known. In addition, I have also prepared, for the first time, some diacyl derivatives of the aminophenols. These substances are also, of course, secondary bases, and their ability to condense with camphoroxalic acid was likewise investigated. The results of the work on the preparation and properties of ortho- and paraminophenol and their mono and diacyl derivatives, including a description of some unsuccessful experiments on the preparation of triacyl derivatives of these phenols are now given in the third section of this dissertation.

ACYL DERIVATIVES OF ORTHO- AND PARAMINO- PHENOL.

A study of the literature relating to ortho- and paraminophenol and a considerable number of their acyl derivatives

¹ Ber. d. chem. Ges., 11, 232.

shows that the recorded methods of preparing some of their compounds are not always consistent with each other. I have found that in certain cases it was advisable to modify a published procedure in order to obtain a good yield, and that the properties of several of my products differ from those given in the literature. Moreover, I have synthesized a number of acyl derivatives which have not hitherto been described.

The first step in my work was the conversion of ortho- and paranitrophenol into the corresponding monoacetylaminophenols. Of the methods which have been suggested for this purpose, that of Morse,¹ which consists in reducing the nitrophenols by means of acetic acid and tin, appeared to be the most convenient, but Zincke and Hebebrand² state that it failed to give them the desired compounds. Professor Morse informs me that he has received, in private communications, similar statements from other chemists, but that in the hands of certain workers the method has given complete satisfaction. He suggested that these conflicting experiences might be accounted for by variation in the concentration of the acetic acid which was employed, and that the best results would be obtained by the use of absolutely anhydrous acetic acid. Accordingly, I titrated some of the best glacial acetic acid obtainable and added to it recently distilled acetic anhydride, in quantity exactly sufficient to raise the acid content to 100 per cent. By means of this mixture, and by carefully excluding moisture from the apparatus, I experienced no difficulty in obtaining a yield of each monacetylaminophenol equal to 50 per cent of the theoretical.

By adding concentrated hydrochloric acid in excess, to the crude solution of acetylorthoaminophenol, which is obtained after removal of the tin, and evaporating the mixture to dryness, orthoaminophenol hydrochloride is readily formed.

From acetylorthoaminophenol, m. p. 201°, I prepared the following derivative, by the Schotten-Baumann method:

Dibenzoylorthoaminophenol, $\text{C}_6\text{H}_5\text{COOC}_6\text{H}_4\overset{1}{\text{N}}\overset{2}{\text{H}}\text{COC}_6\text{H}_5$, crys-

¹ Ber. d. chem. Ges., **11**, 232.

² Ann. Chem. (Liebig), **226**, 69.

tallizes from alcohol in slender, white needles, melting at 180° . Its formation in this manner has not been previously recorded; it involves replacement of both acetyl and hydrogen by benzoyl groups.

The preparation of paranitrobenzoyl derivatives was effected by gradually mixing paranitrobenzoyl chloride, dissolved in benzene, with an aqueous solution of orthoaminophenol hydrochloride and adding, at intervals, small quantities of 20 per cent potassium hydroxide solution. The experiment was conducted in an atmosphere of carbon dioxide because free aminophenol is extremely sensitive to oxygen, especially in the presence of alkali. Operating under these conditions, I obtained two compounds, which were separated by means of acetone.

Paranitrobenzoylorthoaminophenol, $\text{HOC}_6\text{H}_4\text{NHCOC}_6\text{H}_4\text{NO}_2$, is deposited from alcohol in small, yellow crystals melting at 220° . It is tolerably readily soluble in acetone.

Diparanitrobenzoylorthoaminophenol, $\text{O}_2\text{NC}_6\text{H}_4\text{COOC}_6\text{H}_4\text{NHCOC}_6\text{H}_4\text{NO}_2$, is practically insoluble in the ordinary organic media. It crystallizes from nitrobenzene in slightly gray, feathery crystals, melting at 219° .

The corresponding metanitrobenzoyl derivatives were obtained in a similar manner to the para compounds.

Metanitrobenzoylorthoaminophenol, $\text{HOC}_6\text{H}_4\text{NHCOC}_6\text{H}_4\text{NO}_2$, is insoluble in benzene, but readily dissolves in hot acetone, from which it is deposited in small, yellow crystals, melting at 206° .

Dimetanitrobenzoylorthoaminophenol, $\text{O}_2\text{NC}_6\text{H}_4\text{COOC}_6\text{H}_4\text{NHCOC}_6\text{H}_4\text{NO}_2$, easily dissolves in benzene at the ordinary temperature and crystallizes from alcohol in light, flaky plates, which melt at 188° .

Under the same conditions as were employed in the case of paranitrobenzoyl chloride, except that the potassium hydroxide solution was only 10 per cent, phenylsulphonic chloride and orthoaminophenol hydrochloride yielded phenyl-

sulphoneorthoaminophenol, $\text{HOC}_6\text{H}_4\text{NHSO}_2\text{C}_6\text{H}_5$. It was deposited from benzene or ether in small needles, which were almost white and melted at 141° . In another experiment, carried out under similar conditions as nearly as they could be reproduced, except that I used a different preparation of phenylsulphonic chloride, I obtained only *diphenylsulphone-orthoaminophenol*, $\text{C}_6\text{H}_5\text{SO}_2\text{OC}_6\text{H}_4\text{NHSO}_2\text{C}_6\text{H}_5$, which was deposited from alcohol in slightly reddish columnar crystals, melting at 134° . Georgesco states¹ that he obtained only diphenylsulphoneorthoaminophenol, m. p. 81° – 83° , from phenylsulphonic chloride and orthoaminophenol, by the Schotten-Baumann reaction, but, in spite of several attempts, I was unable to prepare a compound with this melting point, or to detect its presence in my product. I regret that Georgesco's original paper is not accessible to me.

The formation of acetylparaminophenol from paranitrophenol was effected in the same manner as in the case of the ortho compound. Here, likewise, absolute acetic acid must be employed and moisture excluded from the apparatus. Under these conditions the preparation presents no special difficulties.

I also obtained the compound by the action of tin amalgam on the nitrophenol, in the presence of acetic acid of 100 per cent concentration. The experiments were carried out in an apparatus of special construction,² lent to me by Professor Morse. By means of an electric current the amalgam is produced continuously in the apparatus and various mechanical devices ensure constant contact between fresh amalgam and the nitro compound.

Acetylparaminophenol behaves towards concentrated hydrochloric acid like the ortho compound. It melts at 166° . The melting point, 179° , given by Morse,³ is due to a printer's error. In the course of some experiments with this compound I heated it on the water-bath with alcohol, 95 per cent,

¹ Chem. Centrabl., 1900, I., 543. Bulet. Societati de Stinte, 8, 668.

² Vide H. P. Straus: Diss., Johns Hopkins University, 1905.

³ Ber. d. chem. Ges., 11, 232.

and camphoroxalic acid. The product, after purification by means of ethyl acetate, strongly resembled the original acetaminophenol in its appearance, but melted at 170° instead of 166° . Closely agreeing analyses showed the content of carbon to be 0.5 per cent too high and that of nitrogen 0.9 per cent too low, *vide* p. 64. By heating at 105° the compound lost in weight to the extent of 0.43 per cent and then showed the same composition as at first and also, practically, the original melting point, $166^{\circ}.5$. Such behavior in this substance does not appear to have been observed before. I believe that it can be best explained as follows: A portion of the acetyl derivative is hydrolyzed by the water in the alcohol, under the catalytic influence of the camphoroxalic acid, and the mixture, or solid solution of acetyl derivative and aminophenol combines with some ethyl acetate. As this latter is not present in the crystals in any simple molecular ratio, it is probably to be regarded more as a solid solution than as ethyl acetate of crystallization. During the heating process acetylation once more takes place, by the action of free acetic acid present in the ethyl acetate and so, in this way and by the elimination of ethyl acetate, the original substance is regenerated.

By the action of acetyl chloride I obtained the diacetyl derivative, $\text{CH}_3\text{COOC}_6\text{H}_4\text{NHCOCH}_3$, m. p. 150° , which has been described by Ladenburg,¹ whose method of preparation is much less convenient.

Benzoyl chloride reacts with acetylparaminophenol under the conditions of the Schotten-Baumann method, yielding

N-Acetyl-*O*-benzoylparaminophenol,

$\text{C}_6\text{H}_5\text{COOC}_6\text{H}_4\text{NHCOCH}_3$, which is deposited from alcohol in white, feathery crystals, melting at $166^{\circ}.5$. This difference in the action of benzoyl chloride on the ortho- and paracetylaminophenols is interesting and suggestive (*vide* p. 50).

Shortly after this work was completed Reverdin² published a description of *O*-acetyl-*N*-benzoylparaminophenol and of

¹ Ber. d. chem. Ges., **9**, 1529.

² *Ibid.*, **39**, 3794 (1906).

O-benzoyl-*N*-acetylparaminophenol. Both compounds are stated to melt at 171°. I sent a specimen of my compound to Professor Reverdin and he was good enough to forward me a specimen of his substance. A direct comparison of both preparations was made by each of us and it was found that the differences in the m. p. was due to the different thermometers which we employed.¹

Albert W. Smith, who prepared benzoylparaminophenol by the action of phosphorus pentachloride on *syn*-hydroxybenzophenoneoxime and also from benzoyl chloride and paraminophenol, gives the melting point as 205°–207°.² My substance, also made from benzoyl chloride, melted at 227°.5.

When paranitrobenzoyl chloride is allowed to react with paraminophenol hydrochloride, under conditions similar to those described for the ortho compound (p. 51), two substances are formed: *Paranitrobenzoylparaminophenol*,



is deposited from alcohol in small, glistening, orange-red, monoclinic crystals, melting at 258°. *Diparanitrobenzoylparaminophenol*,



is obtained from solution in nitrobenzene in light yellow, microscopic crystals, melting at 264°.

Metanitrobenzoyl chloride also yields two compounds:

Metanitrobenzoylparaminophenol, $\overset{1}{\text{HOC}}_6\text{H}_4\overset{4}{\text{NHCOC}}_6\text{H}_4\overset{1}{\text{NO}}_2$,

which crystallizes from acetone in slender, light yellow needles, melting at 215°–216°. *Dimetanitrobenzoylparaminophenol*,

$\overset{3}{\text{O}}_2\text{NC}_6\text{H}_4\overset{1}{\text{COOC}}_6\text{H}_4\overset{4}{\text{NHCOC}}_6\text{H}_4\overset{3}{\text{NO}}_2$, is deposited from nitrobenzene as a light gray powder, melting at 264°–265°.

The action of phenylsulphonic chloride on paranitrophenol was studied under conditions similar to those employed with orthoaminophenol. Under these circumstances I obtained

only *phenylsulphoneparaminophenol*, $\overset{1}{\text{HOC}}_6\text{H}_4\overset{4}{\text{NHSO}}_2\text{C}_6\text{H}_5$,

¹ Ber. d. chem. Ges., **40**, 2849 (1907).

² *Ibid.*, **24**, 4042 (1891).

which crystallizes from benzene in slender, slightly colored needles, melting at 156°.5. Georgesco¹ states that he obtained this compound and also diphenylsulphoneparaminophenol,



and gives the melting point of the former as 125°–126° and the latter as 150°–152°. I have repeated my experiments several times and, in the absence of details regarding the conditions which he used, I can only suggest, as the probable cause of the discrepancy between his results and mine, that he failed to purify his substances; this would explain why my *mono*-sulphone melts more than 4° higher than his *di*-sulphone. The analytical figures for my compound are given in the latter part of the present section. It may also be pointed out, in support of the correctness of my results, that they agree in every way with those reported by Troeger and Uhlmann² for the paratolylsulphones. They also obtained only monosulphones of ortho- and paraminophenol. Moreover, their ortho compound melts at 138°–139°, a little below the para derivative, which melts at 143°; the melting points of my compounds, 141° and 156°.5, respectively, correspond closely to these and show the same relationship. For convenience of comparison and by way of a summary, I show in the following table the simpler mono and diacyl derivatives of ortho- and paraminophenol. I have tried to make the list complete. The figures represent the melting points of the respective compounds. Those described for the first time in this dissertation are given in *italics*. It will be noticed that out of a total of 30 substances included in the table, 12 have been prepared for the first time by me; of the remaining 18 I have prepared 2 by a new, simpler method, have shown that the existence of 2 is decidedly doubtful, and have corrected the melting point of another one:

¹ *Loc. cit.*

² J. prakt. Chem., (2), 51, 438, 441 (1895).

Table Showing the Simpler Acyl Derivatives of Oriho- and Paraminophenol.

Name of acyl radical	Orthoaminophenol. Monacyl derivative.	Diacyl derivative.	Monacyl derivative.	Diacyl derivative.
Acetyl	201°	123°-124°	166°	150°
Acetyl-benzol				166° .5
Acetyl-ethylsulphonyl				136°
Acetyl-picryl				165°
Acryl	123°-124° 167°		227° .5 ²	233°-234° 171°
Benzoyl		180° ¹		
Benzoyl-acetyl				
Chloracetyl	136° 206°	188°	215°-216° 89°-90°	264°-265°
Metanitrobenzoyl			258°	264°
Methyl-sulphonyl		219°	143°	
Paranitrobenzoyl	220°		156° .5	
Paratolylsulphonyl	138°-139° 141°	81°-83° ³ 134°	174°	150°-152° ³
Phenylsulphonyl				
Picryl				

¹ Prepared by new method.

² Previous melting point corrected.

³ Existence doubtful.

A number of experiments at 0° , at the ordinary temperature and at 240° – 250° have been made in order to obtain tribenzoyl derivatives of ortho- and paraminophenols. In every case without success.

EXPERIMENTAL.

Preparation of Orthoacetoaminophenol.—Orthonitrophenol (12 grams, 1 mol.) was mixed in a capacious, round-bottomed flask with glacial acetic acid, 50 grams = 10.5 mol., to which sufficient recently distilled acetic anhydride had been added to bring the acid content to 100 per cent. The flask was attached to a long reversed condenser, suitably protected from the moisture of the atmosphere and the contents of the flask were heated until the nitrophenol had dissolved. To this solution granulated tin, 15 grams, was added. The reduction commenced immediately and the action quickly became very vigorous. It is desirable to allow the reaction to proceed as rapidly as it is possible without loss of substance. As soon as the action moderates, a second portion of tin, 15 grams, is added and, if necessary, external heat is applied to bring practically all of the metal into solution. The liquid is now poured into 2 liters of water, the mixture warmed and a current of hydrogen sulphide passed into it until no further precipitate of stannous sulphide takes place. Sometimes it is convenient to filter the liquid through cheese cloth before all the tin has been thrown down and then, later, to make a final filtration through paper.

The clear filtrate is concentrated until crystals appear; after being cooled and crystals are drained and recrystallized twice from 95 per cent alcohol. The compound melts at 201° , as stated by Morse¹ and Ladenburg.¹ The yield is 40–45 per cent of the theoretical.

Preparation of Orthoaminophenol Hydrochloride.—The compound is obtained readily by adding an equal volume of concentrated hydrochloric acid to the clear filtrate from the stannous sulphide and then evaporating to a small bulk. Should this

¹ *Loc. cit.*

concentrated liquid have the odor of acetic acid, more hydrochloric acid is added and the heating repeated until all acetic acid has been expelled. The hydrochloride readily forms crystals and may be purified by recrystallizing twice from water with the addition of a little animal charcoal. It has no melting point within the range of my thermometers. The yield is about 50 per cent of the theoretical.

Action of Benzoyl Chloride on Orthoacetaminophenol.—The acetaminophenol, 14 grams = 1 mol., was dissolved in warm water and mixed with benzoyl chloride, 20 grams = 1 2/3 mols. The liquids were well shaken and to them was added, in small portions, sufficient aqueous solution of potassium hydroxide, 10 per cent, to produce a permanent alkaline reaction. A precipitate which formed, finally, was removed, washed with water and recrystallized from alcohol. It is deposited in slender, white needles, which melt at 180° and were found to consist of *dibenzoylorthoaminophenol*. The yield was excellent.

Analysis:

I. 0.1455 gram substance gave 0.4032 gram CO₂ and 0.0674 gram H₂O.

II. 0.1822 gram substance gave 7.7 cc. N at 22° and 760 mm.

	Calculated for C ₆ H ₄ $\left\{ \begin{array}{l} \text{OCOC}_6\text{H}_5(1) \\ \text{NHCOC}_6\text{H}_5(2) \end{array} \right.$	Found.	
		I.	II.
C	75.7	75.57	
H	4.73	5.14	
N	4.41		4.65

Action of Paranitrobenzoyl Chloride on Orthoaminophenol Hydrochloride.—Free orthoaminophenol is readily colored by oxygen, consequently, experiments which involve the action of an alkali on the aminophenol hydrochloride were always carried out in an atmosphere of carbon dioxide. Paranitrobenzoyl chloride being a solid, it was found to be most convenient to employ it in benzene solution.

The aminophenol hydrochloride, 5 grams = 1 mol., was dissolved in water and mixed with a benzene solution of para-

nitrobenzoyl chloride, 12.7 grams = 2 mols. Potassium hydroxide, 20 per cent aqueous solution, was added gradually, the mixture being constantly shaken; this was continued until the liquid became permanently alkaline. The precipitate which formed was removed and, after being washed with water and dried, it was placed in a Soxhlet apparatus and extracted with acetone. The portion which dissolved was recrystallized from alcohol. It formed slightly yellow, light, feathery crystals, melting at 220°.

Analysis:

0.1677 gram substance gave 16.2 cc. N at 23° and 764 mm.

	Calculated for	Found.
	$\begin{array}{c} \text{C}_6\text{H}_4 \begin{cases} \text{OH} (1) \\ \text{NHCOC}_6\text{H}_4\text{NO}_2 \end{cases} \\ (2) \quad (1) \quad (4) \end{array}$	I
N	10.85	10.9

These results show that the body is *paranitrobenzoylorthoaminophenol*.

The compound that was insoluble in acetone was recrystallized from nitrobenzene; the deposited crystals were light and feathery. After being washed with benzene, they melted at 219°. The substance, which proved to be *diparanitrobenzoylorthoaminophenol*, is practically insoluble in water, ethyl and methyl alcohols, ether, chloroform, ethyl acetate, benzene, toluene and ligroin.

Analysis:

I. 0.1495 gram substance gave 0.3214 gram CO_2 and 0.0443 gram H_2O .

II. 0.1409 gram substance gave 13 cc. N at 20° and 750 mm.

	Calculated for	Found.	
	$\begin{array}{c} \text{C}_6\text{H}_4 \begin{cases} \text{OCOC}_6\text{H}_4\text{NO}_2 \\ \text{NHCOC}_6\text{H}_4\text{NO}_2 \end{cases} \\ 2 \quad 1 \quad 4 \end{array}$	I.	II.
C	58.96	58.63	...
H	3.19	3.28	
N	10.31		10.4

The total yield of these two compounds was 80–90 per cent of the theoretical, in the ratio of 3 parts mono- : 5 parts of the dinitrobenzoyl derivative.

Action of Metanitrobenzoyl Chloride on Orthoaminophenol Hydrochloride.—The experiments with these compounds were carried out under exactly the same conditions as those with paranitrobenzoyl chloride which are described above. I worked with 10 grams (1 mol.) of the hydrochloride and 21.4 grams (1.7 mol.) of the acid chloride. The product of the reaction was extracted with benzene in a Soxhlet apparatus. The residue, insoluble in benzene, was dissolved in acetone, from which it separated in small, yellowish crystals, which melted at 206° and were found to consist of *metanitrobenzoyl-orthoaminophenol*.

Analysis:

I. 0.1541 gram substance gave 0.3434 gram CO₂ and 0.600 gram H₂O.

II. 0.1108 gram substance gave 10.6 cc. N at 24° and 758 mm.

	Calculated for OH(1) $\text{C}_6\text{H}_4\text{NHCOC}_6\text{H}_4\text{NO}_2$ 2 1 3	I.	Found.	II.
C	60.46	60.77		
H	3.87	4.32		
N	10.85			10.69

The second product of the reaction, which was soluble in benzene, was purified by solution in alcohol, from which it was deposited in light, feathery crystals with a slight pinkish tinge. It melted at 186° and proved to be *dimetanitrobenzoylorthoaminophenol*.

Analysis:

I. 0.1165 gram substance gave 0.2504 gram CO₂ and 0.0418 gram H₂O.

II. 0.1307 gram substance gave 12.2 cc. N at 23° and 759 mm.

	Calculated for		Found.
	$\begin{array}{c} \text{C}_6\text{H}_4 \begin{cases} \text{OCOC}_6\text{H}_4\text{NO}_2 \\ \text{NHCOC}_6\text{H}_4\text{NO}_2 \end{cases} \\ \begin{array}{ccc} 1 & 1 & 3 \\ 2 & 1 & 3 \end{array} \end{array}$	I.	II.
C	58.96	58.61	
H	3.19	3.98	
N	10.31		10.5

The total yield of these two compounds was about 80-90 per cent of the theoretical, of which rather more than half consisted of the dinitrobenzoyl derivative.

Action of Phenylsulphonic Chloride on Orthoaminophenol Hydrochloride.—These experiments were carried out under similar conditions to those employed in the case of paranitrobenzoyl chloride (*vide* p. 58). It was, of course, unnecessary to use benzene. I took 5 grams (1 mol.) of the hydrochloride and 21 grams (2 mols.) of the sulphonic chloride in each experiment; the concentration of the potassium hydroxide solution was 10 per cent. The crude, solid product of the reaction was dried and extracted with benzene in a Soxhlet apparatus, to remove a small quantity of a tarry matter. After evaporation of the benzene the material which had dissolved in it was recrystallized from ether, being deposited in slender, pale pink crystals, which are readily soluble in alcohol and melt at 141°. It proved to be *phenylsulphoneorthoaminophenol*. The yield of purified product was about 70 per cent of the theoretical.

Analysis:

I. 0.1101 gram substance gave 0.2346 gram CO₂ and 0.0469 gram H₂O.

II. 0.1347 gram substance gave 6.8 cc. N at 24°.5 and 763 mm.

III. 0.2302 gram substance gave 0.2216 gram BaSO₄.

	Calculated for		Found.
	$\begin{array}{c} \text{C}_6\text{H}_4 \begin{cases} \text{OH}(1) \\ \text{NHSO}_2\text{C}_6\text{H}_4(2) \end{cases} \end{array}$	I.	II. III.
C	57.83	58.14	
H	4.41	4.73	
N	5.5		5.51
S	12.88		 13.22

In another series of experiments in which I used 2.9 grams (1 mol.) of orthoaminophenol hydrochloride and 4 grams of phenylsulphonic chloride (1.25 mol.) with 10 per cent potassium hydroxide, the other conditions being as nearly as possible identical with those described above, I obtained only *diphenylsulphoneorthoaminophenol*. In other experiments in which the proportions of reacting substances were exactly the same as those used in the preparation of the monosulphone, I again obtained merely the disubstituted compound. The only cause of this difference in behavior, which I have been able to detect, is in the phenylsulphonic chloride, two samples of which were at my disposal. Both of these were in Kahlbaum's original packages, but one always gave me the mono- and the other the disubstituted compound. This latter substance crystallizes from alcohol in reddish rods, which melt at 134°.

Analysis:

I. 0.1476 gram substance gave 0.2939 gram CO₂ and 0.0582 gram H₂O.

II. 0.2029 gram substance gave 6.5 cc. N at 24° and 751 mm.

III. 0.2174 gram substance gave 0.2548 gram BaSO₄.

IV. 0.1532 gram substance gave 0.1786 gram BaSO₄.

	Calculated for C ₆ H ₄ $\left\{ \begin{array}{l} \text{OSO}_2\text{C}_6\text{H}_5(1) \\ \text{NHSO}_2\text{C}_6\text{H}_5(2) \end{array} \right.$	Found.			
		I.	II.	III.	IV.
C	55.49	55.23			
H	3.85	4.38			
N	3.59		3.46		
S	16.47			16.10	16.01

A number of experiments were also made with a third sample of phenylsulphonic chloride, which was likewise one of Kahlbaum's preparations. It had been in stock for some time before I used it. With orthoaminophenol hydrochloride and this compound I obtained what appeared to be mixtures of the mono- and disulphones, melting at 126°.8. The monosulphone melts at 141° and the disubstituted compound at

134°. Mixtures of the two melt at 118° and a mixture of monosulphone and of the third preparation mentioned above (m. p. 126°.8) melts at 121°.

The discrepancy between my results and those of Georgesco has already been pointed out (*vide* p. 52). I made several attempts to prepare his diphenylsulphone derivative by varying the experimental conditions and the proportion of phenylsulphonic chloride, but without success. The low melting point of Georgesco's disulphone, 81°–83°, and its red color, make me very doubtful as to the purity of his substance.

Preparation of Paracetoaminophenol.—This compound was prepared from paranitrophenol exactly in the same manner as the ortho derivative (p. 57). A few experiments were made for me by Dr. C. W. Gray to determine whether it was advantageous to prepare paracetoaminophenol by the electrolytic reduction of paranitrophenol in acetic solution. As will be apparent from what follows, the ordinary meaning of the term "electrolytic reduction" is hardly applicable to the conditions under which I worked; the active reducing agent was tin amalgam, which was produced continuously under the influence of the electric current. Paranitrophenol, 9 grams, and acetic acid of 100 per cent concentration, 35 grams, were placed in the cathode vessel. A rod of pure tin was inserted into the anode department. The two vessels were connected by means of mercury and the whole apparatus was mounted on a wooden stand, to which could be imparted an automatic, steady rocking motion. This apparatus was designed by Professor Morse and is practically identical with that fully described and illustrated by H. P. Strauss,¹ who worked under his direction. By the use of a graphite-coated electric furnace, constructed according to the description of Morse and Frazer,² the cathode compartment could be heated to any desired temperature.

The reduction of the nitrophenol proceeded without difficulty under these conditions, and the product of the reaction was worked up in the same manner as that obtained by the

¹ Dissertation, Johns Hopkins University, 1905.

² Am. Chem. J., **32**, 930 (1904).

use of acetic acid and granulated tin. The yield was about 40 per cent of the theoretical.

This acetyl derivative was purified by solution in water, from which it is deposited in colorless, well-formed, monoclinic crystals. These melt at 166° , as given by Friedlander.¹ Because of the varying statements in the literature regarding the melting point of this compound, it was further identified by analysis.

I. 0.1891 gram substance gave 0.4403 gram CO_2 and 0.1019 gram H_2O .

II. 0.2104 gram substance gave 17.8 cc. N at 20° and 767 mm.

	Calculated for $\text{C}_6\text{H}_4\begin{matrix} \text{OH}(1) \\ \text{NHCOCCH}_3(4) \end{matrix}$	Found.	
		I.	II.
C	63.57	63.44	...
H	5.96	5.98	...
N	9.27		9.6

The yield was about 47 per cent of the theoretical.

In the course of some experiments with this substance, I had occasion to heat it on the water-bath with a solution of camphoroxalic acid, in 95 per cent alcohol. A crystalline product was obtained which closely resembled paracetaminophenol, but melted at 170° .

Analysis:

I. 0.1343 gram substance gave 0.3150 gram CO_2 and 0.0716 gram H_2O .

II. 0.1429 gram substance gave 0.3357 gram CO_2 and 0.0766 gram H_2O .

III. 0.2843 gram substance gave 21.5 cc. N at $22^{\circ}.5$ and 760 mm.

IV. 0.1765 gram substance gave 13.3 cc. N at $21^{\circ}.5$ and 755 mm.

	Calculated for		Found.			
	$\text{C}_6\text{H}_4\begin{matrix} \text{OH}(1) \\ \text{NHCOCCH}_3(4) \end{matrix}$	$\text{C}_6\text{H}_4\begin{matrix} \text{OH}(1) \\ \text{NH}_2(4) \end{matrix}$	I.	II.	III.	IV.
C	63.57	66.05	64.09	64.07		
H	5.96	6.42	5.92	5.95		
N	9.27	12.84			8.35	8.32

¹ *Loc. cit.*

A portion of the compound was heated at 105° until its weight became constant. The loss in weight amounted to 0.43 per cent. After this heating the substance melted at $166^{\circ}.5$ instead of 170° and, when analyzed, proved to be paracetaminophenol.

Analysis:

I. 0.1346 gram substance gave 0.3138 gram CO_2 and 0.0742 gram H_2O .

II. 0.2101 gram substance gave 17.5 cc. N at 20° and 752 mm.

	Calculated for $\text{C}_6\text{H}_4\begin{cases} \text{OH}(1) \\ \text{NHCOC}\dot{\text{H}}_3(4) \end{cases}$	Found.	
		I.	II.
C	63.57	63.58	
H	5.96	6.12	
N	9.27		9.24

As stated more fully in the theoretical portion of this paper, I believe that the changes described above are due to the hydrolysis of a portion of the acetaminophenol; this would raise the carbon content; the percentage of nitrogen would, however, be reduced on account of the ethyl acetate which was retained, whereas this would produce much less effect on the carbon and hydrogen values. During the heating to drive off this ethyl acetate, acetylation of the hydrolyzed product took place, so that, finally, I obtained acetaminophenol regenerated in a state of purity.

Preparation of Paraminophenol Hydrochloride.—The salt is readily prepared by adding to the clear filtrate from the stannous sulphide precipitate an equal volume of concentrated hydrochloric acid and evaporating to dryness. Should acetic acid be present towards the completion of the evaporation, more hydrochloric acid must be added and the heating continued. The product is purified by recrystallizing once or twice from water, in the presence of a little animal charcoal. The yield of purified substance is about 45–50 per cent of the theoretical.

Action of Acetyl Chloride on Paracetaminophenol.—When these compounds are mixed, in equimolecular proportions,

and gently heated, they react quickly. The product was crystallized from water. It melted at 150° and corresponded, in general properties, with the substance prepared by Ladenburg¹ from paraminophenol and acetic anhydride. The yield was practically quantitative.

Action of Benzoyl Chloride on Paracetaminophenol.—The experiments with these compounds were carried out under similar conditions to those employed in the case of ortho-aminophenol. I worked in aqueous solution and used 10 per cent potassium hydroxide. The chloride and the acetaminophenol were employed in equimolecular proportion. The product of the reaction separated as a solid; after being washed it was recrystallized from alcohol, from which it was deposited in white, feathery crystals, melting at $166^{\circ}.5$. It is sparingly soluble in hot water but practically insoluble in cold. The compound proved to be *N*-acetyl-*O*-benzoyl paraminophenol. The yield was about 90 per cent of the theoretical.

Analysis:

I. 0.1699 gram substance gave 0.4392 gram CO_2 and 0.0787 gram H_2O .

II. 0.1017 gram substance gave 5 cc. N at $19^{\circ}.5$ and 752 mm.

	Calculated for $\text{C}_6\text{H}_4 \begin{cases} \text{OCOC}_6\text{H}_5(1) \\ \text{NHCOC}_2\text{H}_5(4) \end{cases}$	Found.	
		I.	II.
C	70.58	70.44	...
H	5.09	5.14	...
N	5.49	...	5.58

Action of Paranitrobenzoyl Chloride on Paraminophenol Hydrochloride.—These substances were allowed to react under conditions similar to those employed in the case of ortho-aminophenol. The quantities taken were 5 grams (1 mol.) of the hydrochloride and 16 grams (2.5 mol.) of the acid chloride. The solid product was washed with water, dried and extracted in a Soxhlet apparatus with acetone. The greater portion remained undissolved. The substance soluble in

¹ *Ann. d. chem. Ges.*, 9, 1529 (1876).

acetone did not dissolve at all readily in ethyl alcohol, but it was deposited from methyl alcohol in small orange-red crystals, melting at 258° . It also dissolves in ethyl acetate. I obtained the same compound, as the only product of the reaction, by intimately mixing finely divided paraminophenol hydrochloride, 3 grams (1 mol.), with the acid chloride, 4.2 grams (1.1 mol.), and heating in an open vessel at 160° . The resulting material was titrated in a mortar with 10 per cent sodium carbonate solution and then recrystallized from alcohol. The compound proved to be paranitrobenzoylparaminophenol.

Analysis:

I. 0.1384 gram substance gave 0.3067 gram CO_2 and 0.0548 gram H_2O .

II. 0.1852 gram substance gave 18.1 cc. N at $23^{\circ}.5$ and 770 mm.

	Calculated for	Found.	
	$\text{C}_6\text{H}_4 \begin{matrix} \text{OH}(1) \\ \text{NHCOC}_6\text{H}_4\text{NO}_2 \\ 4 \quad 1 \quad 4 \end{matrix}$	I.	II.
C	60.46	60.43	
H	3.87	4.39	
N	10.85		10.85

That portion of the product of the Schotten-Baumann reaction which was insoluble in acetone was crystallized from nitrobenzene; it formed a light yellow powder, melting at 264° . It did not dissolve in water, ethyl alcohol, ether, methyl alcohol, ethyl acetate, not in hot or cold aqueous potassium hydroxide solution. The substance proved to be *diparanitrobenzoylparaminophenol*.

Analysis;

I. 0.1067 gram substance gave 0.2312 gram CO_2 and 0.0343 gram H_2O .

II. 0.2285 gram substance gave 21 cc. N at 21° and 751 mm.

	Calculated for $\begin{array}{c} 11 \quad 4 \\ \text{OCOC}_6\text{H}_4\text{NO}_2 \\ \text{C}_6\text{H}_4 \diagdown \\ \text{NHCOC}_6\text{H}_4\text{NO}_2 \\ 4 \quad 1 \quad 4 \end{array}$	Found.	
		I.	II.
C	58.96	59.09	
H	3.19	3.57	
N	10.31		10.12

The total yield of these compounds was about 80–90 per cent of the theoretical, in the proportion of approximately 3 parts of the mono- : 5 parts of the diacyl derivative.

Action of Metanitrobenzoyl Chloride on Paraminophenol Hydrochloride.—The hydrochloride, 5 grams (1 mol.), in aqueous solution, was mixed with the acid chloride, 12.8 grams (2 mols.), dissolved in benzene, and aqueous potassium hydroxide, 20 per cent solution was added. The conditions of the experiment were exactly like those described for paranitrobenzoyl chloride and orthoaminophenol hydrochloride (*vide* p. 58). The solid product of the reaction, after being washed with water and dried, was extracted in a Soxhlet apparatus with ethyl acetate. The portion which dissolved in this solvent crystallized from acetone in slender, light yellow needles, melting at 215°–216°. It was sparingly soluble in alcohol and proved to be *metanitrobenzoylparaminophenol*.

Analysis:

0.1612 gram substance gave 0.3588 gram CO₂ and 0.0627 gram H₂O.

	Calculated for $\begin{array}{c} 1 \\ \text{OH} \\ \text{C}_6\text{H}_4 \diagdown \\ \text{NHCOC}_6\text{H}_4\text{NO}_2 \\ 4 \quad 1 \quad 4 \end{array}$	Found.
C	60.46	60.70
H	3.87	4.32

That portion of the reaction product which did not dissolve in ethyl acetate was purified by solution in nitrobenzene, from which it was deposited as a gray powder, melting at 264°–265°. It was insoluble in all the ordinary organic media and consisted of *dimetanitrobenzoylparaminophenol*.

Analysis:

I. 0.1764 gram substance gave 0.3824 gram CO_2 and 0.0599 gram H_2O .

II. 0.2342 gram substance gave 22.6 cc. N at 26° and 760 mm.

	Calculated for		Found.
	$\begin{array}{c} \text{C}_6\text{H}_4 \begin{array}{l} \nearrow \text{OCOC}_6\text{H}_4\text{NO}_2 \\ \searrow \text{NHCOC}_6\text{H}_4\text{NO}_2 \end{array} \end{array}$	I.	II.
C	58.96	59.12	
H	3.19	3.77	
N	10.31		10.39

The total yield of these two compounds was 80-90 per cent of the theoretical, in the ratio of about 1 part mono- : 2 parts of dimetanitrobenzoyl derivative.

Action of Phenylsulphonic Chloride on Paraminophenol Hydrochloride.—The work with these substances was carried out exactly as in the case of the corresponding experiments with orthoaminophenol (*vide* p. 61). The quantities employed were 5 grams (1 mol.) of the hydrochloride and 12 grams (2 mols.) of the acid chloride. The solid product of the reaction was treated with benzene; a small portion of insoluble tarry matter remained. The part which dissolved was crystallized from ether and deposited in slender, white needles, melting at $156^\circ.5$. It is readily soluble in alcohol, and consisted entirely of *phenylsulphoneparaminophenol*, irrespective of which of the three samples of sulphonic chloride was employed, *vide* p. 62. An experiment was made with a different proportion of sulphonic chloride, but the product was identical with the one first obtained.

Analysis:

I. 0.1201 gram substance gave 0.2555 gram CO_2 and 0.0542 gram H_2O .

II. 0.1642 gram substance gave 8.3 cc. N at 27° and 758 mm.

III. 0.2301 gram substance gave 0.2189 gram BaSO_4 .

IV. 0.2202 gram substance gave 0.2086 gram BaSO_4 .

Calculated for		Found.			
$\begin{array}{c} \text{C}_6\text{H}_5 \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{NHSO}_2\text{C}_6\text{H}_5 \end{array} \end{array}$		I.	II.	III.	IV.
C	57.85	58.01			
H	4.41	5.01			
N	5.5		5.45		
S	12.88			12.01	13.01

The yield was 70-80 per cent of the theoretical.

All my efforts to prepare a diphenylsulphone were unsuccessful.

Mr. Marshall P. Cram has been good enough to carry out for me a number of experiments with the object of obtaining *triacyl derivatives* of ortho- and paraminophenol. As his efforts have, unfortunately, not been attended with success, they will be described very briefly. Orthoaminophenol hydrochloride, 7.25 grams (1 mol.), and benzoyl chloride, 50 grams (7 mol.), were mixed and treated with potassium hydroxide, 23 grams (8 mol.), in 15 per cent aqueous solution. The mixture was allowed to remain at the ordinary temperature for 3 weeks. In a second experiment, similar to the above, the materials were allowed to remain for 3 weeks at 0°. Two further experiments were made at the ordinary temperature and at 0°, respectively, using pyridine, 100 cc., instead of the potassium hydroxide. Finally, all four experiments were repeated with paraminophenol hydrochloride instead of the ortho compound. The products from the experiments with potassium hydroxide were poured into water, filtered and recrystallized from benzene. Only the dibenzoylaminophenols were obtained. From the aqueous filtrate benzoic acid alone could be isolated. The product from the pyridine experiments was extracted with ether, washed with water and the residue crystallized from benzene; it proved to be the dibenzoyl compound. The ethereal solution was extracted with dilute sulphuric acid and then evaporated; the residue was a mixture of benzoic acid and monobenzoylaminophenol.

Experiments were next tried at a high temperature. Dibenzoylparaminophenol, 72 grams, was mixed with dehydra-

ted sodium benzoate, 2.7 grams, a drop of concentrated sulphuric acid and a large excess of benzoyl chloride, 11.4 grams, and heated in a sealed tube for 1.5 working days, at 240° . A portion which was removed and tested showed that no reaction had taken place, consequently the heating was continued for another day at 250° . This treatment caused incipient decomposition. Only the unchanged disubstitution derivative could be obtained from the product. A similar experiment was made with dibenzoylorthoaminophenol, but the conditions of heating were 1.5 days, at 240° . The result was similar to that obtained with the para compound.

CONCLUSIONS.

1. In the preceding pages I have given an account of the study of a number of new compounds prepared from camphoroxalic acid and certain primary amines.

2. Many new compounds are also described resulting from the action of a number of secondary amines on camphoroxalic acid.

3. Various new salts of this acid with several tertiary bases are also described. Some of these are well defined and highly crystalline.

4. An improvement of Morse's method of preparing ortho- and paraminophenol has been worked out.

5. A considerable number of new mono- and diacyl derivatives of each of these phenols are described.

6. Other acyl derivatives of the phenols have been made by simpler and better methods than those hitherto employed. In some instances the statements in the chemical literature regarding their properties have been shown to be incorrect. Fresh data have been supplied and the existence of certain compounds has been proved to be very doubtful.

BIOGRAPHICAL.

Leon F. Williams was born near Gatesville, Gates County, North Carolina, on August 27, 1881. His preparation for college was received in the Academy of that place. In the fall of 1896 he entered Trinity College, North Carolina, from which he received the degree of Bachelor of Arts in 1901 and the degree of Master of Arts in 1902. During the last two years of his stay he was assistant in the Department of Chemistry. Since 1902 he has been a graduate student in Chemistry in the Johns Hopkins University, his subordinate subjects being physical chemistry and mineralogy. Throughout his connection with the University he has held a North Carolina Hopkins scholarship.

